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HETEROCYCLES IN FOCUS

Modern methods for the synthesis of indolo[2,3-*b*]quinoxalines (microreview)

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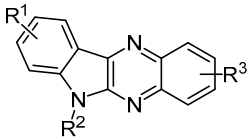


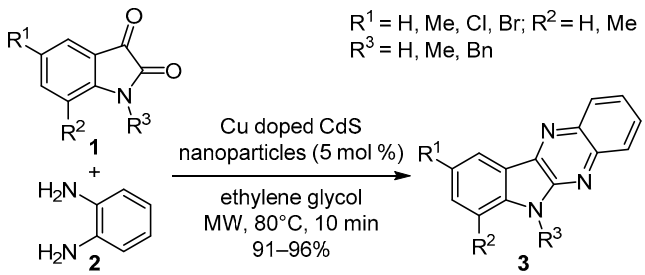
In this minireview, we cover new methods for the synthesis of indolo[2,3-*b*]quinoxaline derivatives that have been published over the previous decade. The majority of the approaches reported in the literature rely on transition-metal-catalyzed cross-coupling reactions and direct C–H functionalization, as well as intramolecular oxidative cyclodehydrogenation processes (S_N^H reactions).

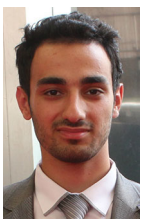
Introduction

Indoloquinoxalines are a widespread class of heterocyclic compounds that attract significant attention of researchers due to their many applications in materials science and medicinal chemistry. For instance, many indolo[2,3-*b*]-quinoxaline derivatives are used in various optoelectronic devices as sensitizers,[1] semiconductors,[2–4] light-emitting[5–7] and sensor materials.[8] The indolo[2,3-*b*]quinoxaline framework is a common structural motif in numerous biologically active compounds that exhibit antiviral,[9,10] antitumor,[11–13] and antidiabetic[14] activity. The current minireview refers to the most significant publications describing new methods for the synthesis of indolo[2,3-*b*]-quinoxaline derivatives, published over the years 2012–2022.

Condensation and cycloaddition reactions

The most frequently employed synthetic route to indolo-[2,3-*b*]quinoxaline derivatives relies on the condensation reactions of isatin with *o*-phenylenediamine.[15,16] The usual catalysts in such reactions are Brønsted acids, for example, acetic, formic, or hydrochloric acid.[17] The use of copper-doped CdS nanoparticles was recently proposed for the reactions of substituted isatins **1** with *o*-phenylenediamine (**2**), performed under the conditions of microwave irradiation.[15] Cerium(IV) oxide nanoparticles could be used equally well, showing effectiveness in analogous reaction that proceeded in aqueous medium and led to products **3** in up to 96% yields.[16]





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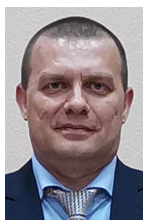

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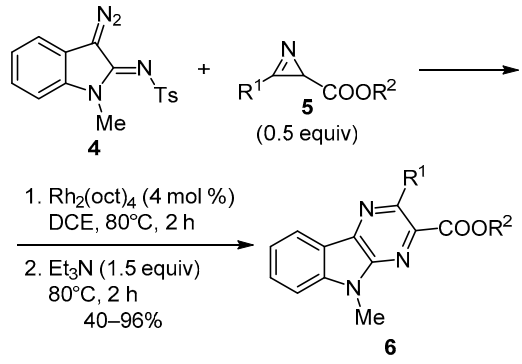
Condensation and cycloaddition reactions (continued)

There is no information on the synthesis of indolo[2,3-*b*]-quinoxaline derivatives *via* the condensation of *in situ* generated 2,3-diaminoindole with α-dicarbonyl compounds, even though this reaction has been effective and convenient as one of the routes for the preparation of pyrazino[2,3-*b*]indole derivatives.[18]

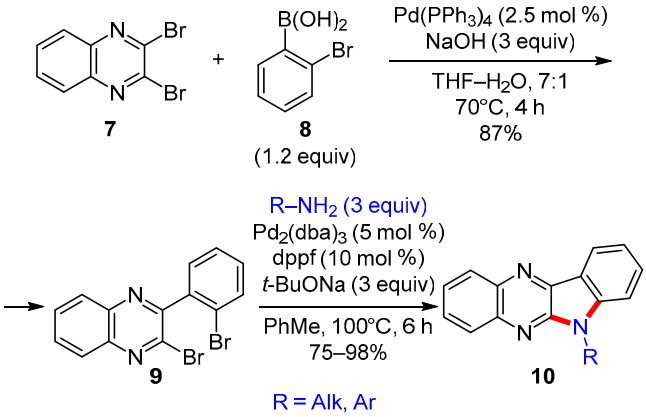
The main limitation of these methods, as a rule, is the generation of a mixture containing regioisomeric indoloquinoxalines when using unsymmetrical *o*-phenylenediamines or α-dicarbonyl compounds. An effective method has been described in the literature for regioselective synthesis of pyrazino[2,3-*b*]indole derivatives **6** representing the central structural motif of indolo[2,3-*b*]quinoxaline framework. This method consists of a rhodium-catalyzed formal [3+3] cycloaddition followed by aromatization of 3-diazoindolin-2-imine **4** with a wide range of azirines **5**.[19] The same synthetic approach was applied to the reactions of 3-diazoindolin-2-imine **4** with β-enaminoesters, enabling a substantial extension of the series of 5*H*-pyrazino[2,3-*b*]indole derivatives that were obtained in high yields.[20]



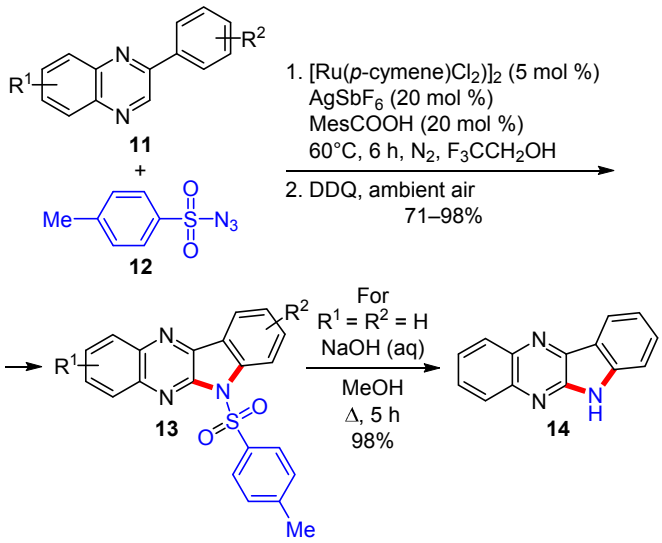
R^1 = Me, 2-thiophenyl, 2-furyl, Ph, $O_2NC_6H_4$, 3-MeC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 4-IC_6H_4, 4-$F_3CC_6H_4$, 4-NCC_6H_4
R^2 = Et, *n*-Bu, *t*-Bu

Transition-metal-catalyzed cross-coupling and direct C–H functionalization reactions

The prominence of cross-coupling reactions in the synthesis of indoloquinoxaline and its analogs has been increasing over the last 10 years. As early as 2007, the Ackermann research group proposed a simple and effective approach to the synthesis of fused indole derivatives from secondary amines and 2,3-dibromoquinoxaline, using a one-pot Buchwald–Hartwig amination followed by a direct Pd-catalyzed C–H bond functionalization.[21,22] A logical extension of this method resulted in a new two-step procedure for the preparation of fluorescent indolo-quinoxalines **10** through Suzuki cross coupling of 2,3-dibromoquinoxaline (**7**) with 2-bromophenylboronic acid (**8**), followed by annulation that was accomplished by double C–N coupling of 2-arylquinoxaline dibromo derivative **9** with various primary amines.[23]



A research group from India has proposed in 2021 a new, effective route for obtaining a broad range of biologically active *N*-substituted 6*H*-indolo[2,3-*b*]quinoxalines **13** in up to 98% yields by Ru(II)-catalyzed tandem *ortho*-C–H functionalization reactions of 2-arylquinoxalines **11** with sulfonyl azide **12**, followed by one-pot oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[24] The given method provides access to the corresponding *N*-unsubstituted 6*H*-indolo[2,3-*b*]quinoxalines, due to the possibility of facile detosylation of products **13** by refluxing with dilute NaOH solution in MeOH, as it is clearly demonstrated in the example of obtaining unsubstituted indolo[2,3-*b*]quinoxaline **14**.



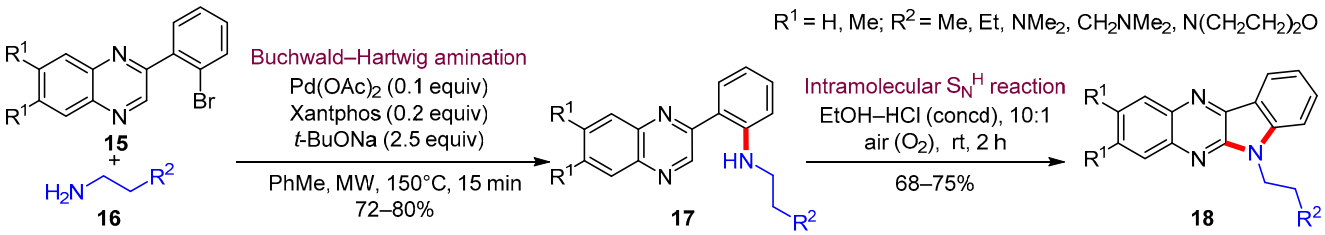
R^1 = H, 7-Cl, 7-Br, 6,7-diMe, 6,7-diMe
R^2 = H, 4-Me, 4-OMe, 4-Et, 4-C_6H_5, 2-F, 4-Cl, 3-Br, 4-CF_3, 4-SO_2Me, 4-OH

Direct C–H functionalization reactions not catalyzed by transition metals

In the modern organic synthesis practice, methods of direct C–H functionalization, complying with the principles of green chemistry, specifically the PASE (pot, atom, and step economic) principle, are increasingly used.[25] One of the synthetic strategies allowing the direct functionalization of a C–H bond is nucleophilic aromatic substitution of hydrogen (S_N^H reactions).[26,27] Within the framework of this methodology, the C–H bond is viewed as a group that inherently susceptible to functionalization, avoiding the need for preliminary introduction of easily substituted nucleofugic groups. This approach provides step, atom, and waste economy route of molecular transformation.

Recently, there was developed convenient synthetic approach for obtaining a wide range of indolo[2,3-*b*]-quinoxalines that possess tuberculostatic properties. This approach employs a combination of Buchwald–Hartwig cross coupling with intramolecular S_N^H reaction.[28] The procedure for the first step involves interaction of the respective substituted 2-(2-bromophenyl)quinoxaline **15** with alkylamines **16** in the presence of a catalytic system consisting of $Pd(OAc)_2$ (10 mol %) and Xantphos (20 mol %) in PhMe, using microwave irradiation for 15 min. The subsequent one-pot treatment of the obtained amino derivative **17** with a 1:10 (v/v) mixture of concentrated HCl and EtOH allowed to achieve an intramolecular nucleophilic aromatic substitution of hydrogen over 2 h at room temperature. The target compounds, indolo[2,3-*b*]-quinoxaline derivatives **18**, including the antiherpetic agent B-220 and its analogs, were obtained in up to 75% yields.

The major advantage of this approach was the possibility of using not only alkylamines, but also anilines, as well as various 2-(*o*-bromoaryl)-1,4-diazines, resulting in the formation of a wide array of heterocyclic indoloquinoxaline analogs.[29]



Conclusion

Thus, it has been shown that modern methods for assembling indolo[2,3-*b*]quinoxaline framework mostly rely on various procedures for direct C–H functionalization either in the presence of transition metal catalysts or without such catalysts. These routes of synthesis provide access to previously unavailable unsymmetrical indoloquinoxaline derivatives and their analogs, the preparation of which *via* traditional condensation reactions would be associated with considerable difficulties.

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