Indole Chemistry

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Direct Oxidative Coupling of *N*-Acetyl Indoles and Phenols for the Synthesis of Benzofuroindolines Related to Phalarine**

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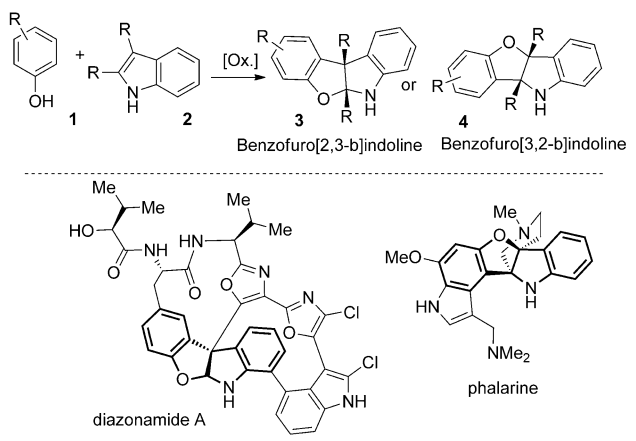
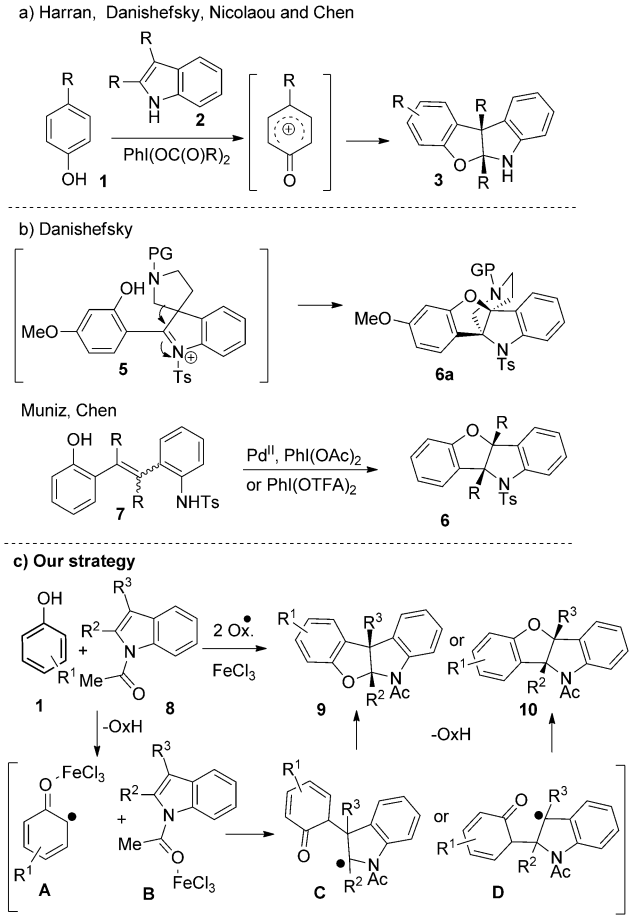
Abstract: *Inspired by the biogenetic synthesis of benzofuroindoline-containing natural products, we designed an oxidative coupling between phenol and N-acetyl indoles. This straightforward and direct radical process, mediated by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and $FeCl_3$ allowed the regioselective synthesis of benzofuro[3,2-b]indolines, whose structure is found in the natural product phalarine.*

The direct oxidative coupling between phenolic and indolic moieties has been thought to be the central part of the biogenetic scenario of the biosynthesis of several natural products which contain benzofuroindoline cores (Scheme 1).[1,2] The union of phenol **1** and indole **2** under oxidative conditions could lead to two regioisomeric adducts: the hemiaminal containing benzofuro[2,3-*b*]indoline **3** or the 1-phenoxy-2-aniline-ethane containing benzofuro[3,2-*b*]indoline **4** (Scheme 1). Benzofuroindoline frameworks of type **3** are found in the diazonamides,[1a,b] azonazine,[1c] bipleiophylline,[1d] voacalgine A,[1e] pleiocraline, and pleiocorine.[1f–h] In contrast, phalarine is the only natural product that displays a benzofuroindoline skeleton of type **4**.[2]

We believe that due to the biosynthetic pathway of oxidative coupling, the benzofuroindoline framework **3** is predominant in nature over skeleton **4**. It is plausible to postulate that the oxidation of the phenol triggers the reaction by generating an electrophilic species.[3b] The nucleophilic character of the indole nucleus would result in the formation of a C–C bond between the C3 and *ortho* position of the indole and the phenol, respectively. Indeed, very elegant biomimetic syntheses of benzofuroindolines of type **3** were inspired by this concept but exhibited limited scope and low yields, e.g., the synthesis of diazonamide A, haplophytine, and azonazine (Scheme 2a).[3] More general multistep methods



Scheme 1. Postulated biogenesis of benzofuroindolines from natural origin.



Scheme 2. Regioselective synthesis of benzofuroindolines and our radical coupling strategy.

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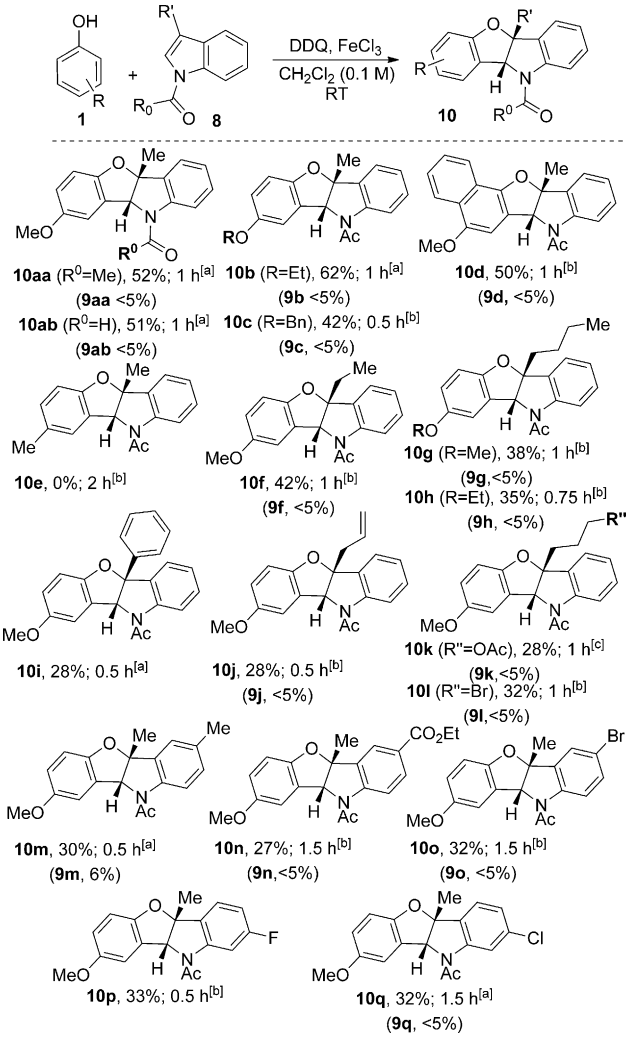
toward these compounds have also been described,[4] including our work.[5a]

The reversal of regioselectivity in the case of phalarine implicated a different pathway. Danishefsky and co-workers investigated the access to the benzofuro[3,2-*b*]indoline core **6a** by direct coupling of phenol and indole without success.[3b] They finally obtained this substructure through the rearrangement of an azaspiroindolenine **5** or a stereospecific Pictet–Spengler reaction to complete the total synthesis of phalarine (Scheme 2b).[6] Inspired by the palladium(II)-catalyzed intramolecular aminoalkoxylation of a stilbene derivative **7** reported by Muniz,[7] the group of Chen realized the formal synthesis of phalarine through a similar transformation mediated by a hypervalent iodine reagent to construct the expected polycycle **6** (Scheme 2b).[8]

We recently engaged a program to explore new methods for the direct coupling of indoles and phenols. In this line, we disclosed the iron(III) chloride promoted C3-regioselective hydroarylation of electrophilic *N*-acetyl indoles **8** by phenols or electron-rich (hetero)aromatic reagents.[5] Subsequent deacetylation and oxidation allowed us to obtain benzofuro-[2,3-*b*]indolines as well as related furoindolines, pyranoindolines, pyrroloindolines, and piperidinoindolines. In continuation of our efforts in this field, we sought to study a direct oxidative phenol–indole cross-coupling[9] involving a radical process.[10] We were inspired by two recent reports from the groups of Lei[11] and Pappo,[12] who described independently the synthesis of 2,3-dihydrobenzofurans through an oxidative cross-coupling of styrenes and phenols, mimicking polyhydroxystilbene's self-merging observed in nature.[13] Both methods use an oxidant (2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or $(t\mathrm{BuO})_2$) to oxidize electron-rich phenols into phenol radicals[14] and a catalytic amount of an iron catalyst to promote the stabilization of the C radical over the O radical. Our challenge was the addition of the electron-rich C radical **A** to the electron-rich indole nucleus.[15] During our work on the C3-regioselective hydroarylation, the activation of *N*-acetyl indole[16,17] with $FeCl_3$ was decisive to turn the indole nucleus into an acceptor **B** of electron-rich aromatic nucleophiles.[5] We postulated that a similar activation will be beneficial to our planned radical process. Therefore, the dual activation of the *N*-acetyl indole and phenol radical by $FeCl_3$ should act in synergy to favor the coupling between the two species **A** and **B** (Scheme 2c). Two radical regioisomeric adducts **C** and **D** could be expected leading to benzofuroindolines **9** and **10**, respectively.

The investigation of the oxidative coupling was conducted with *N*-acetyl-3-methylindole **8aa** and *p*-methoxyphenol **1a** (1.5 equiv). It was found that the $FeCl_3/(t\mathrm{BuO})_2$ system did not afford the desired products, whereas the association of $FeCl_3$ and DDQ led to the regioselective formation of benzofuro[3,2-*b*]indoline **10aa** with only traces of benzofuro-[2,3-*b*]indoline **9aa**.[18,19] DDQ or $FeCl_3$ alone could not promote the oxidative coupling, proving their synergetic effect. After further experimentations,[18] we discovered that it was optimal to run the reaction with stoichiometric amounts of $FeCl_3$ in a 0.1M dichloromethane solution at room temperature to yield 52% of **10aa** (Scheme 3). Evaluation of the influence of the substituent on nitrogen proved that acetyl



Scheme 3. Oxidative coupling between phenols and *N*-acetyl indoles leading to benzofuro[3,2-*b*]indolines. [a] 1.5 equiv phenol, 1.5 equiv DDQ, and 1.1 equiv $FeCl_3$; [b] 3.0 equiv phenol, 3.0 equiv DDQ, and 2.2 equiv $FeCl_3$; [c] 4.0 equiv phenol, 4.2 equiv DDQ, and 2.2 equiv $FeCl_3$.

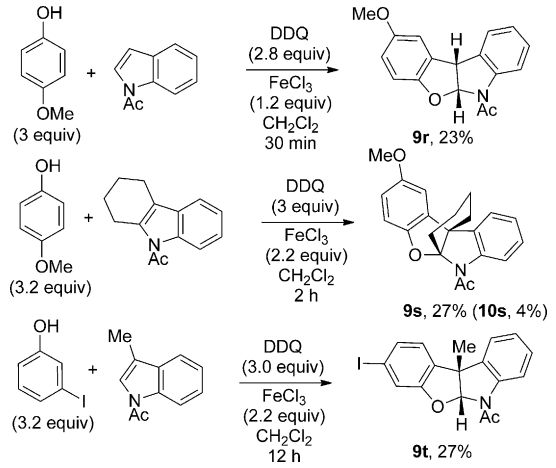
and formyl (**10ab**; 51%) were the optimal activating groups for the fine tuning of the reactivity of the indole nucleus to favor the synthesis of benzofuro[3,2-*b*]indolines **10**.[20] It seems reasonable to postulate that the complexation of $FeCl_3$ by the carbonyl oxygen (intermediate **B**, Scheme 2) might break the aromaticity of the indole nucleus through delocalization of the nitrogen lone pair into the carbonyl π system.[5b] As a consequence, the C2=C3 bond would be less electron-rich and prone to react with radical intermediate **A** (Scheme 2).

Having discovered suitable conditions for the regioselective synthesis of benzofuroindoline **10aa** from *N*-acetyl skatole **8aa** and *p*-methoxyphenol **1a**, we wished to expand the scope of this straightforward oxidative coupling (Scheme 3). Indeed, electron-rich phenols such as *p*-ethoxyphenol, *p*-benzyloxyphenol, and 4-methoxynaphtol afforded the desired benzofuroindolines **10b, 10c**, and **10d** in 62%, 42%, and 50%, respectively. Unfortunately the less electron-

rich *p*-methylphenol did not add to *N*-acetyl skatole (**10e**). Increasing the length of the C3 alkyl chain of the *N*-acetyl indole substrate delivered the desired benzofuroindolines **10f**, **10g**, and **10h** in 42%, 38%, and 35%, respectively, from *p*-methoxyphenol or *p*-ethoxyphenol. The hindered 3-phenyl-*N*-acetyl indole delivered **10i** in 28% yield. Functional groups such as double bond, acetate, or bromide could be present on the C3 alkyl sidechain of indoles and yield adducts **10j–l** in 28–32% yields.[21] Benzofuro[3,2-*b*]indolines were also obtained from indoles with electron-donating (Me, **10m**, 30%) and electron-withdrawing (CO_2Et, **10n**, 27%) groups at C5 as well as halides at C5 (Br, **10o**, 32%) and C6 (F, **10p**, 33%; Cl, **10q**, 32%).

When analyzing the yields, it should be taken into account that we have achieved an unprecedented regioselective one-step oxidative coupling between electron-rich phenols and electron-rich 3-substituted indole nuclei leading to benzofuro[3,2-*b*]indolines. Our straightforward strategy compares favorably with the known methods, which are less convergent and would require several steps to access these regioisomers of benzofuroindolines.[6–8]

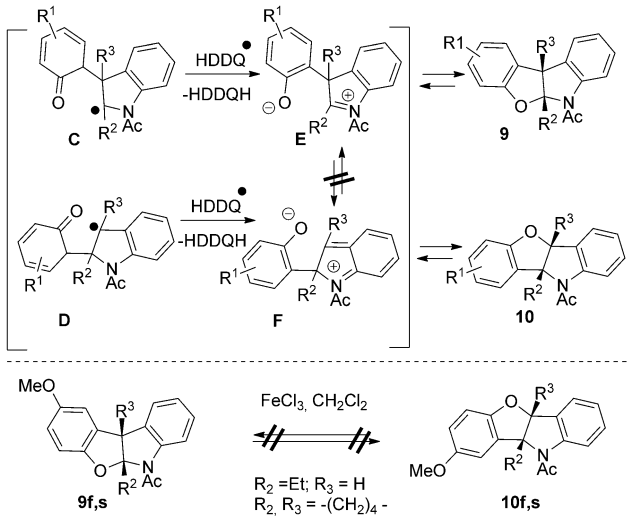
Interestingly, the regioselectivity is inverted with *N*-acetyl indoles, which display the same degree of substitution at the C2 and C3 positions (Scheme 4). The reaction with *N*-acetyl



Scheme 4. Oxidative coupling between phenols and *N*-acetyl indoles leading to benzofuro[2,3-b]indolines.

indole only led to benzofuro[2,3-*b*]indoline **9r** and *N*-acetyl tetrahydrocarbazole gave benzofuro[2,3-*b*]indoline **9s** as the major product with a small amount of the benzofuro[3,2-*b*]indoline **10s**.[18,21] The reaction between *N*-acetyl skatole and the *m*-iodophenol is another case in which only the benzofuro[2,3-*b*]indoline **9t** is formed.

Different mechanistic scenarios were envisioned to explain the formation of benzofuro[2,3-*b*]indolines **10** (Scheme 5): the radical addition of the phenol at C2 (**D** to **F** to **10**) or the radical addition at C3 followed by a 1,2-shift of the phenol part through an iminium intermediate mediated by the presence of Lewis acid in the reaction medium (**C** to **E** to **F** to **10**). An analogous hypothesis could also be postulated to explain the formation of benzofuro[3,2-*b*]indolines **9** (**C** to



Scheme 5. Mechanistic considerations of the regioselectivity.

E to **9** or **D** to **F** to **E** to **9**). The fact that **9f,s** were not converted to **10f,s** when treated with $FeCl_3$ or that **10f,s** did not lead to **9f,s** under the same conditions led us to discard the 1,2-shift pathway and to assume that the observed ratios of **9**/**10** depend on the attack of the phenoxy radical at C2 or C3 of the *N*-acetyl indole.

It is well documented that radicals tend to preferentially add at the C2 position of the indole nucleus, no matter if only the C3 position is substituted or the C2 and C3 positions are unsubstituted,[15,16] which is partly in contrast with our observations. As we reported previously,[5] the combination of *N*-acetyl indoles with $FeCl_3$ seems to strongly modify the reactivity of the indole nucleus: in equally 2,3-disubstituted indoles, the attack of an electron-rich phenol radical at C3 is preferred with our system. However, with 3-monosubstituted *N*-acetyl indoles the attack is predominant at C2: minimization of steric interactions or the stability of the tertiary C3-benzylic radical intermediate **D** over the C2-α-aminoradical **C** might be invoked in the latter case (Scheme 5; $R^3 \neq H$ and $R^2 = H$). The use of less electron-rich phenols such as *m*-iodophenol led to a reversal of the regioselectivity with attack at C3 of 3-monosubstituted *N*-acetyl indoles.

In conclusion, we have accomplished the previously unknown direct oxidative [3+2] coupling between phenol and indole nuclei leading to the regioselective formation of the benzofuro[3,2-*b*]indoline core of phalarine. This radical coupling allows the exquisite union of two aromatic rings known to behave as nucleophiles. The dual activation of both the *N*-acetyl indole and the phenoxyl radical by $FeCl_3$ is crucial for the success of the reaction.

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Keywords: benzofuroindolines · indoles · oxidative coupling · phalarine · phenols

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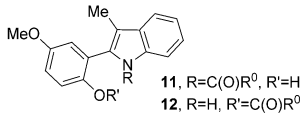
[18] See the Supporting Information.

[19] The byproducts observed were mainly due to the homocoupling of phenols and 2-(2-acetoxyphenyl)indole derivatives **12**, which could be cause from aromatization of **10** by an elimination reaction leading to **11** followed by the migration of the acetyl from the nitrogen to the oxygen.



[20] The more electron-withdrawing *N*-trifluoroacetyl group on 3-methylindole **8ac** did not react under the reaction conditions, whereas a very modest yield of **10ad** (< 5 %) was observed from *N*-benzoyl-3-methylindole **8ad**, along with 2-arylated indoles such as **11ad** and **12ad** (13 % combined) and unreacted **8ad**. *N*-Cbz-3-methylindole **8ae** mainly decomposed under the reaction conditions; *N*-phenylsulfonyl-3-methylindole **8af** was more reactive toward phenol, because all starting material was consumed but led to 2-arylated indole **11af** (23 %, R = SO_2Ph, R′ = H) as the major product and to unidentified compounds.

[21] CCDC 993817 (**10j**), 993820 (**9r**), 993818 (**9s**), 993819 (**9t**), and 1009736 (**11af**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Communications

Indole Chemistry

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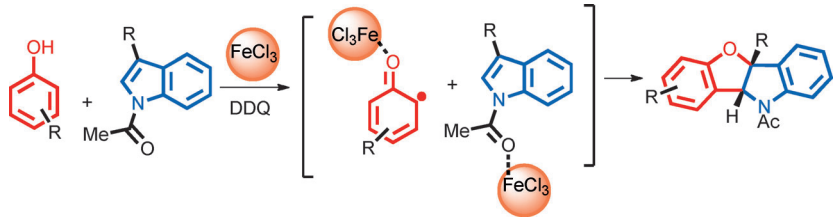
Direct Oxidative Coupling of *N*-Acetyl Indoles and Phenols for the Synthesis of Benzofuroindolines Related to Phalarine



Ironized! The unprecedented direct oxidative coupling between phenols and indole nuclei leading to the regioselective formation of the phalarine benzofuroindoline core is reported through the addition of phenoxy radicals to *N*-acetyl indoles mediated by $FeCl_3$. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.