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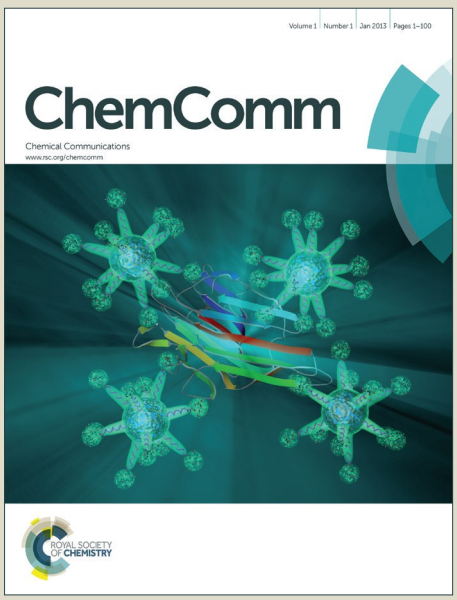

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Journal Name

COMMUNICATION

Synthesis of Benzofuro[3,2-*b*]indoline Amines by a Deamination-Interrupted Fischer Indolization and their Unexpected Reactivity Towards Nucleophiles

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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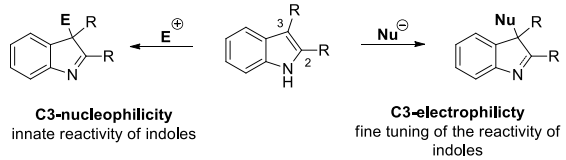
We report the access to the benzofuro[3,2-*b*]indoline framework of phalarine from benzofuran-2-ones via the Fischer indolization reaction which was interrupted at the deamination step. Unexpectedly, allyl nucleophiles did not add to the aminal position of these benzofuro[3,2-*b*]indoline amines but to the adjacent ring junction center in presence of trifluoroborane to deliver 3,3-disubstituted indolines containing a difluoroboron-containing six membered-ring with fluorescent properties.

The C3-nucleophilicity is the predominant character of the indole nucleus.[1] In contrast, the addition of nucleophiles at this C3 position is less common (Scheme 1).[2] Usually this Umpolung of indoles involves an oxidation step to make the C3-position electrophilic.[3] We have also reported a $FeCl_3$-mediated C3-regioselective hydroarylation of N-Ac indoles.[4] During the course of synthetic studies towards the benzofuro[3,2-*b*]indoline motif, we discovered that this scaffold could display an electrophilic character at the C3-position of the indole ring which we would like to report in this communication.

The benzofuro[3,2-*b*]indoline motif is a rare substructure which is found in only one natural product: phalarine (Figure 1).[5] Its regioisomer, the benzofuro[2,3-*b*]indoline skeleton is more present in nature[6]



Scheme 1. C3-nucleophilicity and electrophilicity of indoles.

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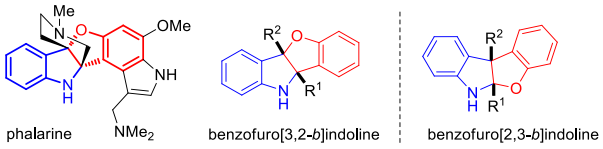
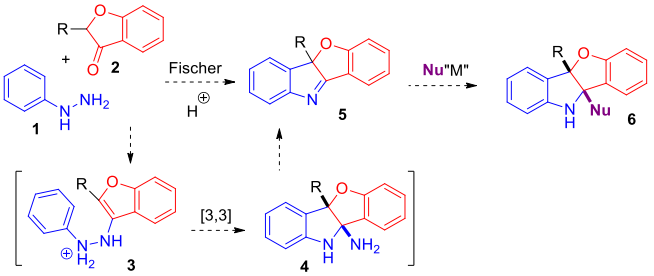


Figure 1 Benzofuroindoline motifs.



Scheme 2 Planned Fischer indolization strategy towards disubstituted benzofuro[3,2-b]indolines.

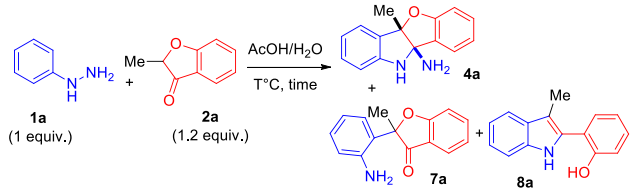
The biogenesis of both these benzofuroindolines is thought to imply an oxidative coupling between an indole and a phenol.[7] Several investigations towards the biomimetic merging of indoles and phenols have been overtaken with success in the case of benzofuro[2,3-*b*]indolines[7,8] including ours.[9] The bioinspired access to the benzofuro[3,2-*b*]indoline motif is more difficult.[7] We recently described an access to this scaffold via a $FeCl_3$/DDQ promoted oxidative coupling[10] which is limited to 3-substituted indoles and therefore unsuited to the synthesis of phalarine.[11] To overcome the issue of regioselectivity of the bioinspired process, we decided to consider a non-biomimetic strategy based on the Fischer indolization from arylhydrazines **1** and benzofuran-3-ones **2** (Scheme 2).[12]

The Fischer synthesis of indoles involves the condensation of a ketone or an aldehyde with an arylhydrazine which is followed by a [3,3]-sigmatropic rearrangement of the resulting ene-hydrazine. Over the years, the Fischer indolization has been employed to the efficient synthesis of functionalized 3,3-disubstituted indolines.[13] If the keto-partner is disubstituted in

alpha of the carbonyl, the sigmatropic rearrangement of **3** lead to a tetrasubstitued carbon at the C3-position which prevent the aromatization into an indole after the elimination of ammonia from **4**. While the formation of 3-alkoxyindoles is known,[14] the synthesis of 3,3-disubstituted indolines incorporating an oxygen substituent at the 3-position from an alpha-oxygenated ketone, as we plan, is more challenging.[15,16] In fact, computational investigations have demonstrated that excessive electron-donation from the substituents of the ene-hydrazine intermediate weaken the N-N bond and could divert the reaction pathway by inducing the dissociation of the N-N bond before the aza-sigmatropic rearrangement.[17] Finally, addition of a nucleophile on the resulting imine of **5**[13l] would deliver a benzofuro[3,2-*b*]indoline **6** with disubstitution across the ring junction.

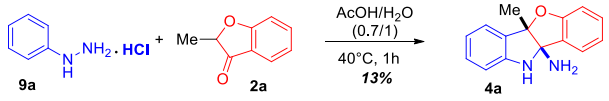
Our investigation started with the reaction between phenyl hydrazine **1a** (1 equiv.) and 2-methylbenzofuran-3-one **2a** (1.2 equiv.). Based on recent reports,[13f,g] we evaluated a 1:1 mixture of acetic acid and water as solvent (Table 1). The reaction at 60°C during 4 hours delivered mainly 2-aryl indole **8a** which results from the Fischer indolization followed by aromatization via a reduction event (entry 1). The reaction at 40°C for 1 hour delivered mainly the 2-arylated-2-methylbenzofuranone **7a** which resulted from the hydrolysis of the Fischer product **5** and was therefore an encouraging result (entry 2). We then modified the ratio of acetic acid and water. A 0.5:1 mixture pleasantly delivered the benzofuro[3,2-*b*]indoline amine **4a** along with **7a** (entry 3). A longer reaction time increased the ratio of undesired **7a** (entry 4). Finally, a 0.7:1 ratio of acetic acid and water was optimal and 88% of the desired Fischer product **4a** was obtained (entry 5). The use of a slight excess of the phenylhydrazine **1a** was detrimental to the yield of **4a** (entry 6).

Table 1 Optimization of the Fischer indolization from phenylhydrazine **1a** and 2-methylbenzofuran-3-one **2a**.



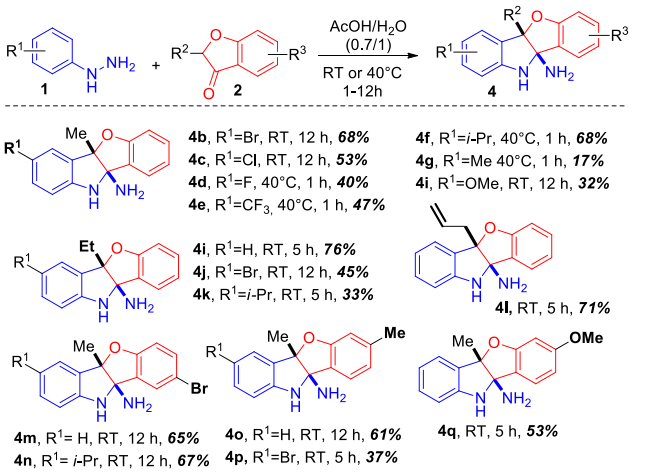
Entry	AcOH/ H_2O	Temp. (°C)	Time (h)	Yield **4a** (%)[a]	Yield **7a** (%)[a]	Yield **8a** (%)[a]
1	1/1	60	4	-	-	80
2	1/1	40	1	-	maj.[b]	-
3	0.5/1	40	1	48	16	-
4	0.5/1	40	2	25	75	-
5	0.7/1	40	1	**88**	9	-
6[c]	0.7/1	40	1	50	10	6

(a) isolated yield. (b) crude NMR ratio. (c) 1.3 equiv. of **1a** and 1 equiv. of **2a**.



Scheme 3 Fischer indolization from the hydrochloride salt **9a** of phenylhydrazine.

Usually, arylhydrazines are commercially available as their hydrochloride salts. Therefore, we studied the reaction between the hydrochloride salt **9a** of phenylhydrazine and 2-methylbenzofuran-3-one **2a** in our optimized conditions and we observed an important drop of the yield (Scheme 3). We think that the use of the hydrochloride salt probably modify the pH of the reaction medium which seems to be important for the outcome of the reaction. Neutralization of the commercial arylhydrazine hydrochloride salts was thus effected before to engage them in the synthesis of benzofuro[3,2-*b*]indolines. In certain cases we observed that it is better to run the reaction at room temperature to avoid the formation of compounds **7** by hydrolysis. The substitution of the phenyl ring of the arylhydrazine partner was first investigated (Scheme 4). *p*-Halogenated hydrazines as well as *p*-trifluoromethylhydrazine furnished the desired benzofuroindolines **4b-e** in 68%, 53% 40% and 47% yields. More electrondonating substituents were then evaluated; *p-iso*-propylhydrazine delivered **4f** in a satisfactory 68% yield while benzofuroindolines **4g** and **4h** from *p*-methyl and *p*-methoxyhydrazines were obtained less efficiently. We then studied the substitution of the benzofuran-3-one.



Scheme 4 Scope of the Fischer indolization for the synthesis of benzofuro[3,2-*b*]indoline amines from benzofuran-3-ones.

Replacing the methyl group at the 2 position by an ethyl or allyl group delivered the desired benzofuroindolines **4i-l** in yields ranging from 33% to 76%. The presence of a bromine, a methyl or methoxy group on the aromatic nucleus of the benzofuranone was also compatible with reaction conditions and benzofuroindolines **4m-q** were formed in 36-67%. It is important to note that we expected to obtain the benzofuro[3,2-*b*]indoline scaffold as benzofuroindolenine **5** or benzofuroindolinol **6** (Nu = OH, Scheme 2) via addition of water, the co-solvent of the reaction, to the imine of **5** which should be formed after elimination of ammonia from the benzofuroindoline amine **4**.[13l] In fact, the benzofuroindoline amine **4** did not undergo elimination of ammonia and was isolated which is an unusual case of interrupted Fischer indolization.[18] The formation of imine **5** is unfavorable because it will hold a double bond at the junction of two fused 5-membered rings and will indeed be highly strained.[18a] The

structures of the benzofuroindoline amine **4e** was confirmed by X-ray crystallography (Figure 2).[19] Moreover, the reaction of benzofuroindoline amine **4a** with methanesulfonyl chloride and triethylamine unusually led to methylsulfonyl methanesulfonamide **10**[20] which structure has been determined by X-Ray crystallography (Figure 2). [19]

Having in hand a straightforward Fischer synthesis of the substituted benzofuroindoline skeleton,[21] we examined the addition of a carbon nucleophile to the aminal position in order to obtain benzofuro[3,2-*b*]indolines **6** disubstituted at the ring junctions (Scheme 2, Nu = CH_2R). Surprisingly, the reaction of **4a** with allyltrimethylsilane in presence of trifluoroborane etherate at room temperature did not delivered the expected compound but the 3,3-disubstituted indoline **11a** in 70% yield and 83% yield with allylmagnesium bromide (Scheme 5). The structure of **11a** was determined by X-Ray analysis.[19] Very interestingly, this compound display a 6 membered-ring containing the imine part of the indolenine and the phenoxy group complexed with a difluoroborane. We can postulate that the first event is the formation of amine borane complex **A**. The formation of an imine is disfavoured at this point.[18a] After elimination of HF from **A**, the aminofluoroborane moiety probably activates the oxygen of the phenoxy group in **B** which triggers the addition of the allyl nucleophile onto the electrophilic tetrasubstituted carbon center adjacent to the aminal. The nucleophile could attack intermediate **C** before the formation of the imine from **D**. Alternatively, the indolenium intermediate **E** could be formed before the addition of the nucleophile (Scheme 6). In summary, an electrophilic character was generated at the C3-position of the indole nucleus.

The Fischer indolization products **4** were engaged in the allylation reaction and transformed into the corresponding boron containing 3,3-disubstituted indolenines **11** (Scheme 5).[22] On the indoline part, bromo (**11b**, 74%), chloro (**11c**, 75%), fluoro (**11d**, 62%) trifluoro (**11e**, 51%), *iso*-propyl (**11f**, 40%), methyl (**11g**, 37%) and methoxy (**11h**, 46%) substituents were tolerated while a bromide could be present on the benzofurane part (**11i**, 68%).

Organodifluoroboron compounds such as Bodipy are widely used as organic fluorescent materials.[23] We therefore wished to evaluate the fluorescent properties of compounds **11a-i**.[24] Low concentration solutions of **11a-i** in dichloromethane display UV absorption maxima around 380 nm and upon photoexcitation at 390 nm, **11a-i** emit fluorescence with maxima around a wavelength of 440 nm.[25]

In conclusion, the Fischer reaction between benzofuran-3-ones and arylhydrazines in mild conditions allowed us to obtain benzofuro[3,2-*b*]indoline amines. This is a very rare synthesis of 3-oxyindoline derivatives via the challenging Fischer indolization in presence of an electrondonating group. During the Fischer reaction, the elimination of ammonia was arrested to avoid the formation of a highly strained imine at the ring junction of the benzofurane and indoline parts. The unfavorable formation of the imine, probably prevents the addition of nucleophiles to the aminal position. In fact, allyl nucleophiles in presence of trifluoroborane could be added to the adjacent tetrasubstituted carbon at the ring junction by activation of the phenoxy substituent. The generation of an electrophilic character at the C3-position of the indole part represent an Umpolung of this nucleus. As a result, we synthesized 3,3-disubstituted indolenines which are related to organic fluorescent materials due to the presence of a difluoroborane-containing six-membered ring.

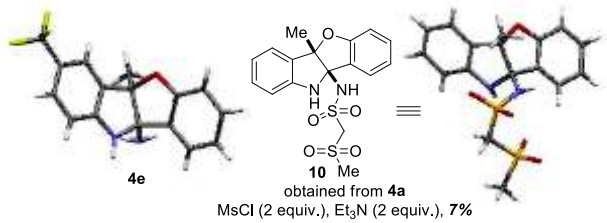
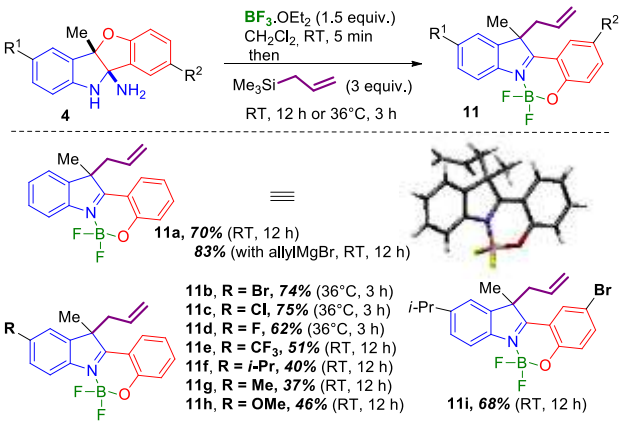
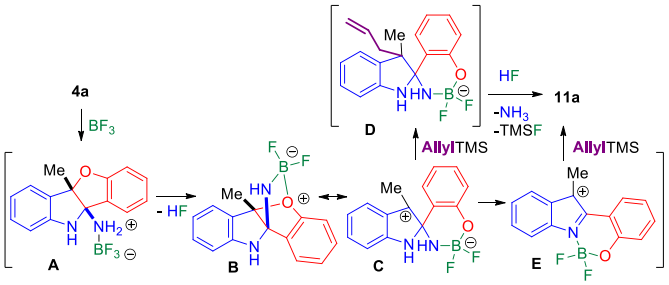


Figure 2 X-Ray structures of benzofuro[3,2-b]indoline amines **4e** and **10**.



Scheme 5 Addition of allyl nucleophiles to the Fischer indolization products.



Scheme 6 Postulated activation of the benzofuro[3,2-b]indoline amines.

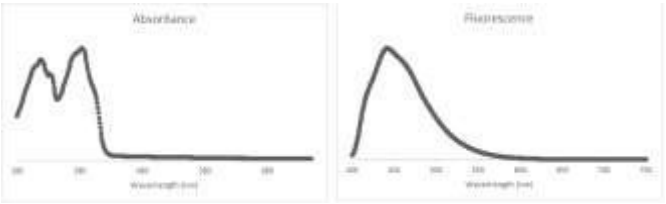


Figure 3 Absorption and fluorescence spectra of **11a** in CH_2Cl_2.

We gratefully acknowledge the ANR (ANR-12-JS07-0002), the Université Paris Sud and the CNRS for financial support. The X-Ray diffractometer was purchased with funds from Région Ile de France (SESAME 2012, 12018501), IUF, LabEx CHARM3AT, Univ. Paris Sud and CNRS. We thank Dr. Anne Léaustic and the LCI (ICMMO) for the use of their spectrophotometer.

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25 Absorption and fluorescence spectra of **11a** are representative of this family of compounds. See the supporting information for spectra of **11b-i.**