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Investigation of the Synthesis of Benzofuroindolines from *N*-Hydroxyindoles: An O-Arylation/[3,3]-Sigmatropic Rearrangement Sequence

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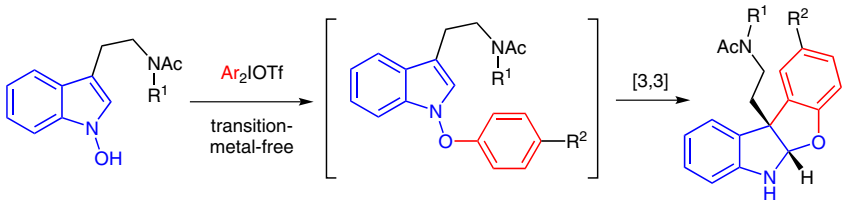
Dedicated to Dr. Patrick Y. S. Lam



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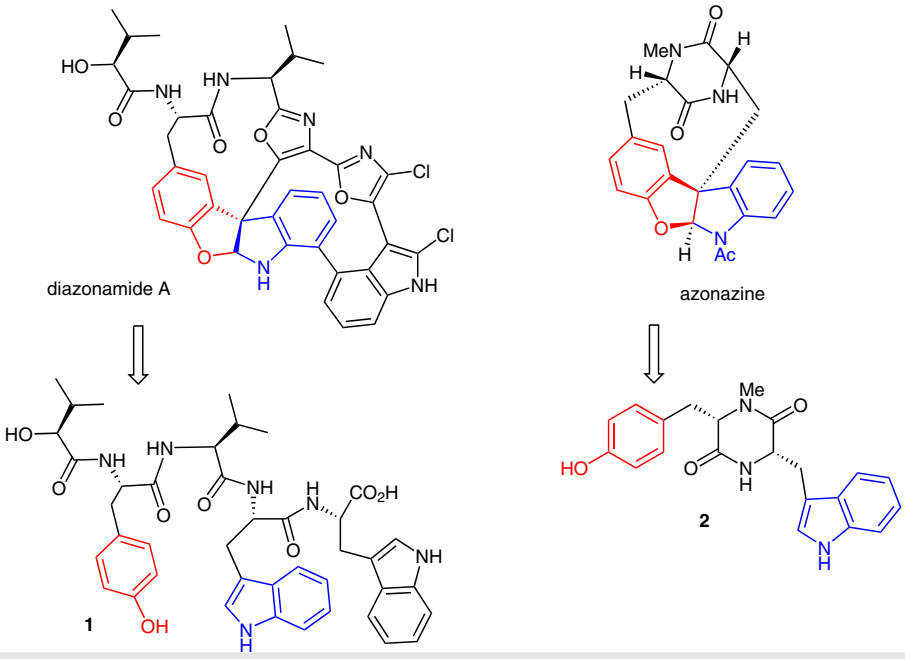
Abstract We report the demonstration that sensitive *N*-hydroxyindoles can be O-arylated under transition-metal-free conditions with biaryliodonium salts. The subsequent spontaneous [3,3]-sigmatropic rearrangement delivers benzofuroindolines derived from tryptamine. We also describe the practical synthesis of *N*-hydroxyindoles by oxidation of indolines with *m*-CPBA.

Key words *N*-hydroxyindoles, diazonamide A, azonazine, benzofuroindoline, [3,3]-sigmatropic rearrangement

Diazonamide A as well as azonazine are benzofuroindoline-containing natural products which have peptidic biogenetic precursors **1** and **2** with tyrosine and tryptophan residues (Scheme 1).[1–3] Diazonamide A displays IC_{50} against several cancer cell lines in the low nanomolar range as well as reduced side effects as demonstrated on mice. This compound seems to target indirectly but specifically the spindle assembly in cancer cells via the inhibition of δ-ornithine aminotransferase (OAT).[1d,e]

The very promising clinical potential against cancer of diazonamide A which contains a benzofuro[2,3-*b*]indoline motif has incited our group to launch a research program



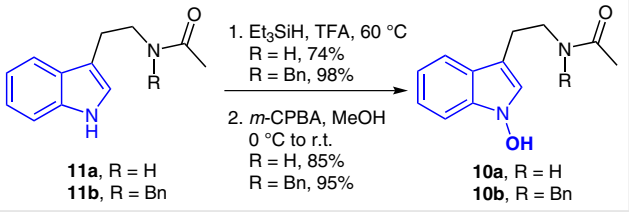
Scheme 1 Diazonamide A, azonazine and their postulated biogenetic peptidic precursors

towards the synthesis of analogues of this natural product. Therefore, we have recently designed new strategies to access the benzofuro[2,3-*b*]indoline core **6** such as the hydroarylation of *N*-acetylindoles **3** by phenols **4** followed by an oxidation stage[4] or the pre-oxidation of indoles **7** into 3-iodoindolines with NIS followed by a silver-mediated coupling with phenols (Scheme 2).[5] Regioisomeric benzofuro[3,2-*b*]indolines **8** were also obtained by the coupling between phenols **4** and *N*-acetylindoles **3** mediated by DDQ and $FeCl_3$.[6]

Unfortunately the strategies we designed are not well suited for the synthesis of compounds derived from tryptamine or tryptophan such as benzofuroindoline **9**, the target of the present communication.[7]

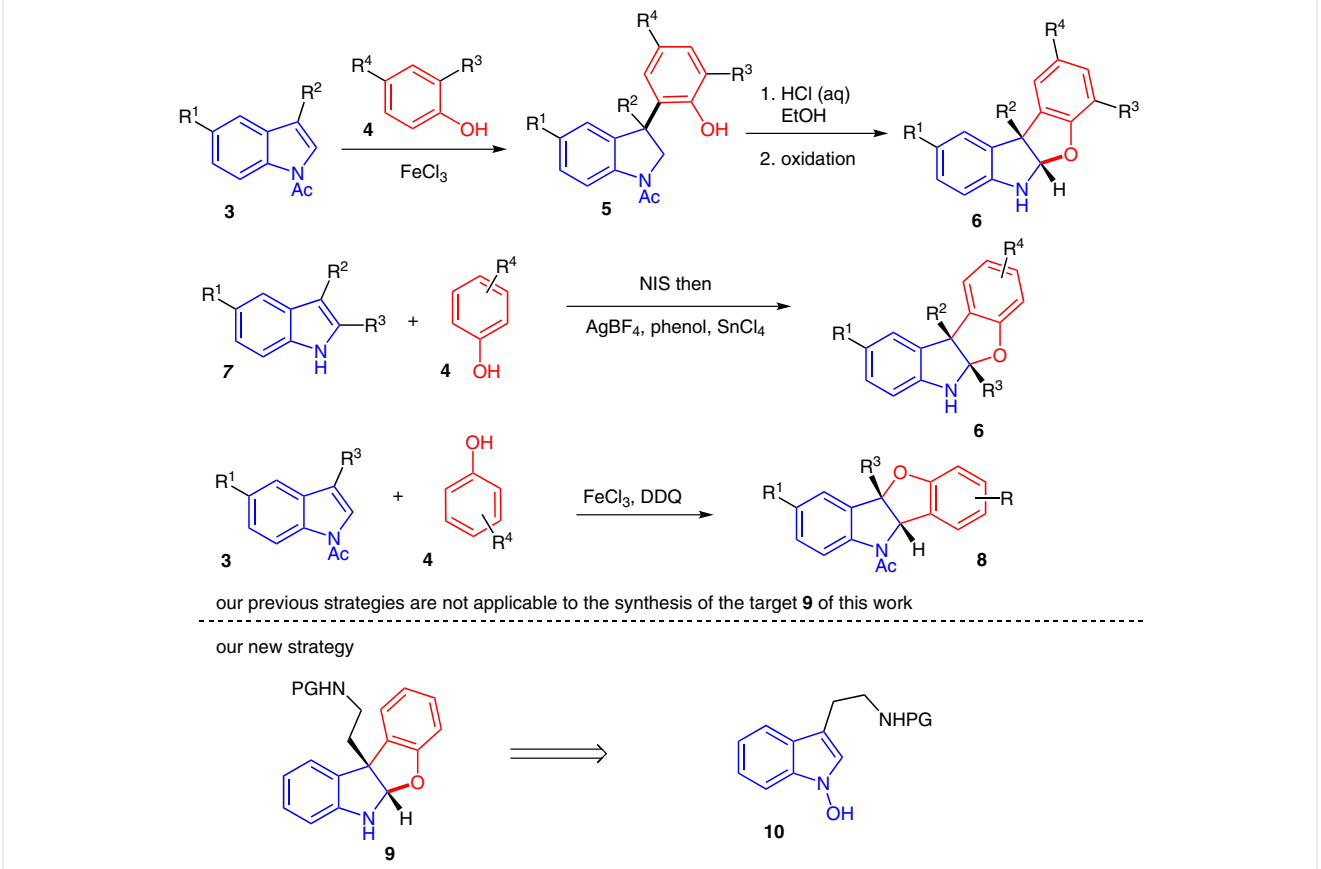
In line with our investigation of electrophilic[8] and/or oxidized indoles and in order to obtain our benzofuroindoline target **9**, we decided to focus our attention on *N*-hydroxyindoles such as **10** which have been extensively studied by Somei and co-workers (Scheme 2).[9]

Several synthetic routes to *N*-hydroxyindoles have been reported.[10] Regarding the synthesis of *N*-hydroxytryptamines **10** or *N*-hydroxytryptophan derivatives, Somei and co-workers described the reduction of the indole nucleus **11** to the corresponding indoline followed by oxidation to the *N*-hydroxyindole catalyzed by a sodium tungstate catalyst in the presence of hydrogen peroxide.[9a,i] We followed Somei's strategy to access *N*-hydroxytryptamine derivatives **10a**,**b** except that we discovered that the oxidation of the indoline to the *N*-hydroxyindole could be performed with *m*-CPBA in methanol which was more convenient and efficient in our hands than the Na_2WO_4/H_2O_2 system (Scheme 3).[11,12]



Scheme 3 Two-stage synthesis of *N*-hydroxyindoles **10** with a *m*-CPBA-mediated oxidation

Having *N*-hydroxyindoles in hand, we then turned our attention to the transformation of *N*-hydroxyindoles **10** into benzofuroindolines **9**.



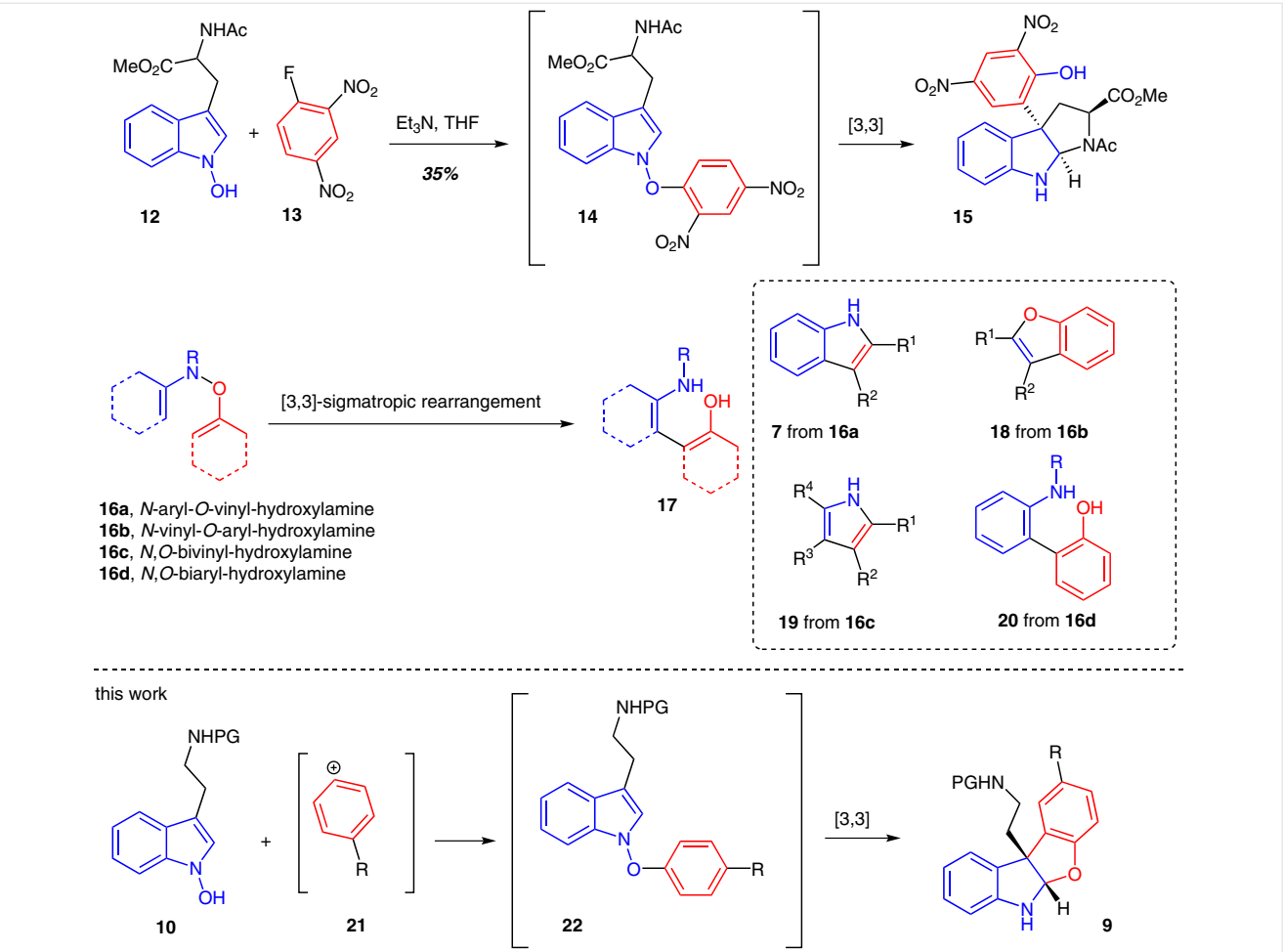
Scheme 2 Our previous synthetic methods towards benzofuroindolines and our new strategy from *N*-hydroxyindoles towards tryptamine-derived benzofuroindolines

We were interested in a report from Somei and coworkers who described an intriguing SNAr reaction of a highly electron-deficient 2,4-dinitrofluorobenzene (**13**) with *N*-hydroxytryptophan derivative **12** which yielded the arylated pyrroloindoline **15** through a [3,3]-sigmatropic rearrangement of transient intermediate **14** (Scheme 4).[9b]

In fact, N,O-disubstituted unsaturated hydroxylamines **16a–d** are known to be unstable and to undergo [3,3]-sigmatropic rearrangement (Scheme 4). For example the Bartoli indole synthesis proceeds by the rearrangement of *N*-aryl-*O*-vinylhydroxylamines **16a** obtained by the addition of vinyl Grignard reagents to nitroarenes.[13] Transient **16a** could also be generated by the O-addition of *N*-arylhydroxylamines to alkynes or allenes[14] or by the Chan–Lam coupling between *N*-arylhydroxylamines and alkenyl boronic acids.[15] Benzofurans **18** are obtained by the rearrangement of *N*-vinyl-*O*-arylhydroxylamines **16b** which could be produced by the condensation of *O*-arylhydroxylamines and ketones,[16] analogous to the Fischer indole synthesis, or by 1,4-addition to α,β-unsaturated *O*-aryloximes[17] or by O-arylation of oximes.[18] The synthesis of pyrroles **19** was described from *N*-*O*-divinylhydroxylamine intermediate **16c** by direct O-vinylation[19] of oximes or isomerisation of *O*-allyl oximes.[20] Recently, the Bartoli reaction has been extended to the synthesis of 2-amino-2′-hydroxy-1,1′-biaryls **20** through the generation of *N*,*O*-diarylhydroxylamines **16d** by addition of aryl Grignard reagents to nitroarenes.[21]

Somei described only one example of the SNAr–sigmatropic rearrangement sequence from *N*-hydroxyindoles. We wished to expand this process to other electrophilic aryl sources **21** (Scheme 4) since the SNAr requires highly electron-deficient fluorobenzene derivatives and/or high temperature and the resulting product is the pyrroloindoline and not the benzofuroindoline probably because the phenol produced is not nucleophilic enough.

Transition-metal-free cross-coupling between biaryliodonium salts and OH-containing substrates[22] including hydroxylamine derivatives or oximes[23] are known. During our own investigations, the groups of Kürti[18] and Olofsson[16f] reported the synthesis of benzofurans by the

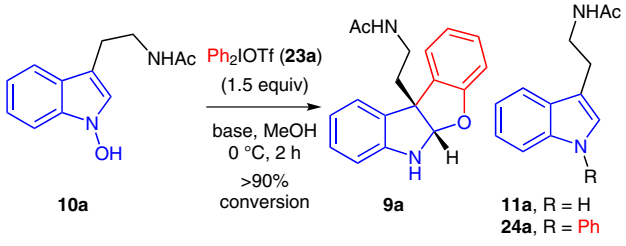


Scheme 4 [3,3]-Sigmatropic rearrangements of hydroxylamine derivatives N,O-disubstituted with unsaturated substituents

metal-free O-arylation of oximes with biaryliodonium salts, followed by a [3,3]-sigmatropic rearrangement of the transient *N*-vinyl-*O*-arylhydroxylamines. These reports prompted us to disclose our preliminary findings in the synthesis of benzofuroindolines via the tandem metal-free O-arylation of *N*-hydroxyindoles with biaryliodonium reagents followed by a [3,3]-sigmatropic rearrangement.

After an extensive screening of reaction conditions we observed that with biphenyliodonium triflate **23a** in MeOH in the presence of base, the desired benzofuroindoline **9a** was formed along with indoles **11a** and **24a** (Table 1). Indole **11a** arose from N–O bond cleavage while **24a** was probably produced by N-arylation of indole **11a**. The difficulty of this process is too keep the N–O bond intact since the *N*-hydroxyindole seems to be sensitive in comparison with other N–O containing substrates towards O-arylation.[14–20,22–26] The mechanism of this N–O bond cleavage is unclear to us. It should be noted that, above 0 °C, the indoles **11a** and **24a** are predominantly obtained and that 1.5 equivalents of the biphenyliodonium triflate were required to ensure a good conversion. Potassium carbonate proved to be the base of choice and the use of 2 equivalents was optimal (Table 1, entries 1–4) since a 1:0.7 ratio of benzofuroindoline **9a** and unwanted indoles (**11a** + **24a**) was obtained. Triethylamine, sodium hydrogenocarbonate and potassium *tert*-butoxide were also able to mediate the formation of benzofuroindoline **9a** (Table 1, entries 5–9).

Table 1 Optimization of the Base for the Synthesis of Benzofuroindoline **9a** by the Metal-Free O-Arylation of *N*-Hydroxyindole **10a** with Biphenyliodonium Triflate **23a**



Entry	Base	Equiv	Ratio **9a**/(**11a** + **24a**)[a]
1	K_2CO_3	0.5	1:2
2	K_2CO_3	1.5	1:1
3	**K_2CO_3**	**2.0**	**1:0.7**
4	K_2CO_3	4.0	complex mixture
5	Et_3N	1.0	1:2
6	Et_3N	1.5	1:0.8
7	Et_3N	2.0	1:1
8	$NaHCO_3$	1.5	1:1.2
9	*t*-BuOK	1.5	1:1.2

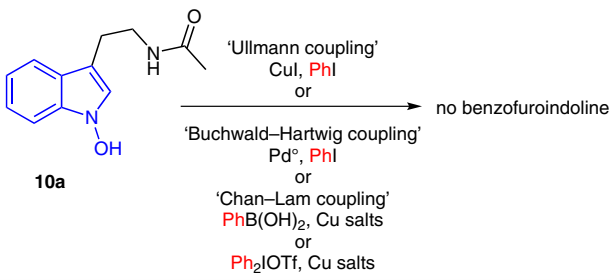
[a] Determined by ^{1}H NMR of the crude.

After the optimization of the ratio of **9a**/(**11a** + **24a**), we noticed that it was best to shorten the reaction time to 30 minutes and to avoid using more than 1.5 equivalents of biaryliodonium triflate **23a** in order to minimize the formation of arylated pyrroloindoline **25** (Table 2). After the O-arylation of the *N*-hydroxyindole **10a** and the sigmatropic rearrangement, benzofuroindoline **9a** and a free phenol-containing pyrroloindoline could be present in equilibrium. The latter could be subjected to the O-arylation of the phenol to yield **25a**. Benzofuroindolines **9a** and **9b** were obtained in combination with **11** and **24** from biphenyliodonium triflate **23a** and bis(4-chlorophenyl)iodonium triflate **23b**, respectively (Table 2, entries 1 and 2).[12]

In order to avoid the formation of pyrroloindolines **25**, the use of a tryptamine-derived *N*-hydroxyindole which does not contain an N–H bond on the side chain was required. Therefore we decided to use *N*-benzyl acetamide **10b** in the O-arylation reaction with biphenyliodonium triflate **23a** or bis(4-chlorophenyl)iodonium triflate **23b** or bis(4-methoxyphenyl)iodonium triflate **23c** (Table 2, entries 3 and 4). Indeed, benzofuroindolines **9c**, **9d** and **9e** were all obtained along with indole **11b**.

Preparative TLC on silica gel allowed us to isolate benzofuroindolines **9a** and **9c** as single components.

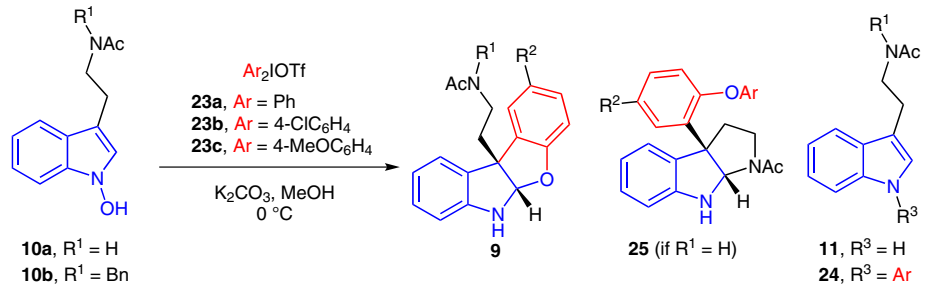
It is interesting to note that we also examined various well-known metal-catalyzed O-arylation reactions such as Ullmann,[24] Buchwald–Hartwig[16d] or Chan–Lam[15,16c,25,26] couplings with **10a** (Scheme 5). Despite extensive efforts, it turned out that the N–O bond of *N*-hydroxyindoles is particularly fragile and no benzofuroindolines were obtained.



Scheme 5 Failed attempts of the O-arylation of *N*-hydroxyindoles by metal-catalyzed coupling reactions

In parallel to the O-arylation/sigmatropic strategy we also investigated the C3-regioselective nucleophilic addition of phenols to *N*-hydroxyindoles. Somei and co-workers have demonstrated that nucleophiles could be added at various positions of *N*-hydroxyindoles.[9] The addition of indoles or pyrroles nucleophiles at C-3 of *N*-hydroxyindoles by mesylation is noteworthy (cf **26a** and **26b**, Scheme 6).[9c,h] We therefore studied the addition of *p*-methylphenol or *p*-methylanisole **4** to *N*-hydroxyindole **9a** in the presence of mesyl chloride without success (Scheme 6). Further investi-

Table 2 Metal-Free Synthesis of Benzofuroindolines **9** from *N*-Hydroxyindoles **10** and Biaryliodonium Triflates **23**



10a, R^1 = H
10b, R^1 = Bn

9

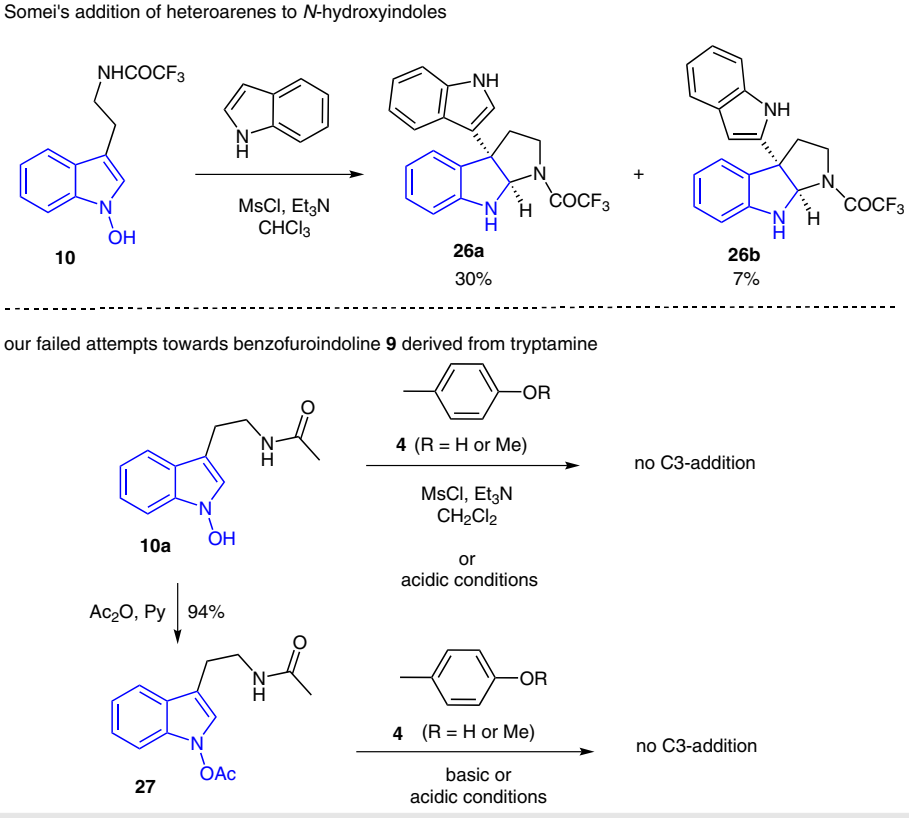
25 (if R^1 = H)

11, R^3 = H
24, R^3 = Ar

Entry	R^1	R^2	**9**	Yields of **9**/(**11** + **24**) (isolated as mixture)	**25**	Yield of **25**
1	H	H	**9a**	44%/36%	**25a**	20%
2	H	Cl	**9b**	22%/40%	**25b**	trace
3	Bn	H	**9c**	17%/41%	–	–
4	Bn	Cl	**9d**	18%/30%	–	–
5	Bn	OMe	**9e**	15%/27%	–	–

gations of this type of coupling in acidic conditions also met with failure. *O*-Acetyl-*N*-hydroxyindole **27** also did not lead to the desired adducts.

In conclusion, we have investigated the synthesis of *N*-hydroxyindoles and the transformation of these sensitive substrates into tryptamine-derived benzofuroindolines through different approaches. Finally a transition-metal-



Scheme 6 Somei's addition of an indole nucleophile to the C3-position of *N*-hydroxyindole **10** and our failed attempts to add phenol derivatives to *N*-hydroxyindoles

free O-arylation with biaryliodonium salts followed by a spontaneous [3,3]-sigmatropic rearrangement delivered the desired targets that we could not access with our previous methodologies.[4–7] Improvement of this methodology and application to the synthesis of natural-product-like compounds will be pursued.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380346.

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(12) **General Procedure for the Synthesis of *N*-Hydroxyindoles 10**: Et_3SiH (1.12 mL, 7.00 mmol, 2 equiv) was added to a solution of *N*-acetyltryptamine **11a** (700 mg, 3.50 mmol, 1 equiv) in TFA (10 mL) and the mixture was stirred at 60 °C for 24 h. After evaporation of the solvent, the crude product was made basic by adding sat. $NaHCO_3$ under ice cooling and the mixture was extracted with CH_2Cl_2–MeOH (95:5). The extract was washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography using EtOAc–MeOH (95:5) afforded the indoline as a yellow oil

(528 mg, 2.59 mmol, 74%). This indoline (400 mg, 1.96 mmol, 1 equiv) in MeOH (1.5 mL) was added dropwise to a solution of 70% *m*-CPBA (675 mg, 3.91 mmol, 1.4 equiv) in MeOH (1.5 mL) at 0 °C. The mixture was then warmed slowly to r.t. and stirred for 12 h. Flash column chromatography purification (100% EtOAc) led to *N*-hydroxyindole **10a** as a white solid (364 mg, 1.67 mmol, 85%); R_f = 0.41 (MeOH–EtOAc, 5:95).

***N*-Hydroxyindole 10a**: ^{1}H NMR (250 MHz, MeOD): δ = 8.07 (br s, 1 H), 7.52 (d, *J* = 9.5 Hz, 1 H), 7.34 (d, *J* = 9.5 Hz, 1 H), 7.14 (t, *J* = 6.7 Hz, 1 H), 7.11 (s, 1 H), 7.00 (t, *J* = 6.6 Hz, 1 H), 3.44 (t, *J* = 7.2 Hz, 2 H), 2.90 (t, *J* = 7.3 Hz, 2 H), 1.91 (s, 3 H). ^{13}C NMR (90 MHz, MeOD): δ = 173.4, 135.8, 125.2, 124.5, 122.8, 119.8, 119.6, 109.4, 108.9, 41.7, 26.1, 22.7. IR (KBr): 3250, 3105, 1680, 1619, 1602, 1580, 743 cm^{-1}. HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $[C_{12}H_{15}N_2O_2]^+$: 219.1089; found: 219.1128.

General Procedure for the Synthesis of Benzofuroindolines 9: To a solution of *N*-hydroxyindole **10a** (50 mg, 0.229 mmol, 1 equiv) in MeOH (1 mL), K_2CO_3 (45 mg, 0.326 mmol, 1.4 equiv) and then Ph_2IOTf **23a** (153 mg, 0.356 mmol, 1.5 equiv) were added at 0 °C and the reaction mixture was stirred for 2 h at 0 °C. Flash column chromatography purification (cyclohexane–EtOAc: 60:40 → 40:60) led to **25a** (14 mg of pyrroloindoline, 20%) and 70 mg of a (1:0.7:0.4 ratio) mixture of benzofuroindoline **9a** (44%), indoles **11a** and **24a** (36%). Preparative TLC on silica gel (MeOH–EtOAc, 5:95) of the mixture allowed the isolation of benzofuroindoline **9a** as a single product. **Benzofuroindoline 9a**: R_f = 0.37 (MeOH–EtOAc, 5:95). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 7.2 Hz, 1 H), 7.18 (d, *J* = 7.3 Hz, 1 H), 7.06 (q, *J* = 7.9 Hz, 2 H), 6.87 (t, *J* = 7.0 Hz, 1 H), 6.77 (t, *J* = 7.2 Hz, 2 H), 6.65 (d, *J* = 7.9 Hz, 1 H), 6.27 (d, *J* = 2.5 Hz, 1 H), 5.25 (br s, 1 H, NH), 3.20 (q, *J* = 6.7 Hz, 2 H), 2.25–2.40 (m, 2 H), 1.79 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 158.7, 155.8, 147.5, 136.6, 128.6, 123.0, 122.3, 121.3, 119.8, 115.8, 110.0, 109.8, 101.8, 59.1, 36.6, 35.5, 23.3. IR (NaCl): 3033, 2960, 1691, 1599, 1492, 1426, 1378, 912, 753 cm^{-1}. HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $[C_{18}H_{19}N_2O_2]^+$: 295.1441; found: 295.1447.

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