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Synthesis of Naked Amino-Pyrroloindoline via Direct Aminocyclization of Tryptamine†

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The first direct access to unprotected amino-pyrroloindoline via aminocyclization of tryptamine and tryptophan has been described. A variety of structurally diverse amino-pyrroloindolines are furnished by use of *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) as the nitrogen source in the presence of catalytic $Rh_2(esp)_2$.

The cyclotryptamine alkaloids are an array of indole alkaloids with promising biological activities.[1] The synthetic challenges posed by the complex structure of cyclotryptamine alkaloids have inspired numerous elegant strategies for building up sterically encumbered quaternary carbon center.[2] To streamline the synthesis of oligomers such as (-)-Chimonanthine, Movassaghi and co-workers have reported Co(I)-mediated homodimerization of 3-bromo-pyrroloindoline[2f] and direct heterodimerization via photo-induced fragmentation of diazene,[2g] which was prepared from the unprotected amino-pyrroloindoline in 4 steps. The diazene-based strategy is more appealing since not only C_{3a}-$C_{3a'}$ bond could be directly connected, but it is also applicable for the construction of diaryl quaternary carbon center.[2g] Additionally, 3-amino-pyrroloindoline is also a key intermediate for the synthesis of cyclotryptamine alkaloids with N_1-$C_{3a'}$ bond linkage (e.g. Psychotrimine).[3] Shishido et al have elaborated it to advanced synthetic intermediate of Psychotrimine via Pd catalyzed double cross coupling.[3e]

As a consequence, the synthesis of amino-pyrroloindoline is of considerable significance and has made great progress. For example, substitution of bromo-pyrroloindoline with azide was adopted in Movassaghi's report.[2g] Later, the same group also developed a C-H amination reaction of pyrroloindoline derived from tryptophan to give amino-pyrroloindoline scaffold.[4o] Dauben found that Rhodium catalyzed nitrene transfer enabled direct aminocyclization of tryptamine in moderate yields.[4a] Yoon also developed oxyamination of tryptamine catalyzed by $CuCl_2$ followed by hydrolysis to prepare amino-pyrroloindoline moiety.[4b]

Very recently, organocatalyzed amino-cyclization of tryptamine was also described to construct enantioenriched amino-pyrroloindolines.[4d,4e] However, those procedures are rather tedious as additional functional group transformations or protecting group manipulations are generally required to achieve the resulting naked amines. In this context, a step-economic synthesis of unprotected 3-amino-pyrroloindoline scaffold is still highly desirable toward the ideal synthesis of cyclotryptamine alkaloids.

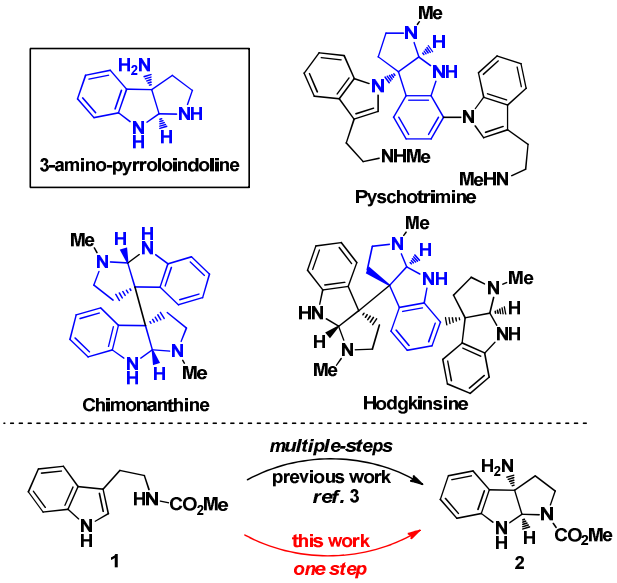
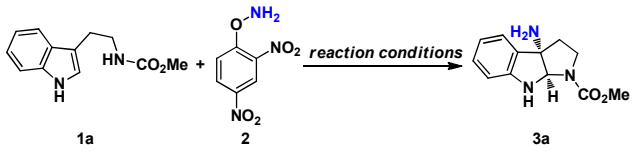


Figure 1. 3-Amino-pyrroloindoline, a key intermediate *en route* to cyclotryptamine alkaloids.

Recently, Kurti and Zhu revealed that 4-(dinitrophenyl)hydroxylamine (DPH) is a powerful amination reagent for converting phenylboronic acid to aniline under

transition-metal free conditions.[5b] Based on this observation, DPH is also amenable for the preparation of unprotected aziridine from alkene catalyzed by $Rh_2(esp)_2$.[5c] In line with our continuing interest in cyclization of tryptamine,[6] herein we disclosed that in the presence of DPH, tryptamine could be directly transformed into naked 3-amino-pyrroloindoline in useful yields.

Table 1. Optimization of reaction conditions[a]



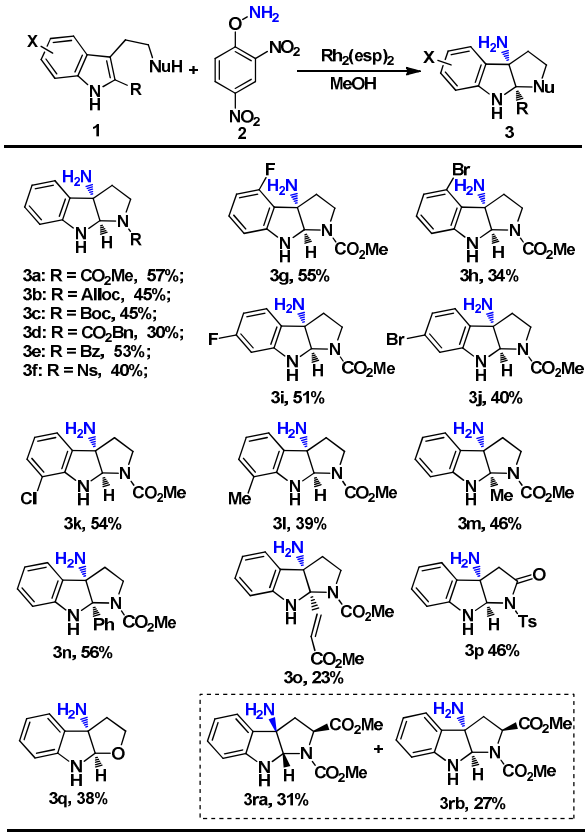
1a 2 3a

entry	catalyst	solvent	T (°C)	*t* (h)	**1a** (%)[b]	yield (%)[b]
1	--	TFE	rt	10	100	0
2	$Rh_2(esp)_2$	TFE	rt	10	30	10
3	$[Rh(OAc)_2]_2$	TFE	rt	10	95	5
4	$[Rh(COD)Cl]_2$	TFE	rt	10	100	0
5	$[Cp^*RhCl_2]_2$	TFE	rt	10	100	0
6	$Sc(OTf)_3$	TFE	rt	10	100	0
7	$Cu(OTf)_2$	TFE	rt	10	95	1
8	$Zn(OTf)_2$	TFE	rt	10	100	0
9	$Pd(OAc)_2$	TFE	rt	10	100	0
10	$Ni(PPh_3)_2Cl_2$	TFE	rt	10	100	0
11	AuCl	TFE	rt	10	100	0
12	$Rh_2(esp)_2$	HFIP	rt	10	30	10
13	$Rh_2(esp)_2$	CH_2Cl_2	rt	10	75	5
14	$Rh_2(esp)_2$	EtOAc	rt	10	70	5
15	$Rh_2(esp)_2$	MeOH	rt	4	15	40
16	$Rh_2(esp)_2$	EtOH	rt	4	30	10
17	$Rh_2(esp)_2$	*i*-PrOH	rt	4	30	5
18	$Rh_2(esp)_2$	MeOH	-20	4	10	50[c]
19	$Rh_2(esp)_2$	MeOH	-20	4	0	57[d]

[a] **1a** (0.1 mmol) in solvent (1 mL) was added to a solution of DPH (0.15 mmol) and $Rh_2(esp)_2$ (2 mmol%) in solvent (1 mL) at indicated temperature. [b] Determined by 1H NMR using 1,4-dimethoxybenzene as inner standard. [c] Isolated yields. [d] **1a** (0.1 mmol) in MeOH (1 mL) was added to a solution of DPH (0.08 mmol) and $Rh_2(esp)_2$ (1 mmol%) in MeOH (1 mL) at -20 °C. After 0.5 h, another mixture of DPH (0.08 mmol) and $Rh_2(esp)_2$ (1 mmol%) was added to the reaction mixture in one portion. TFE = trifluoroacetic acid, HFIP = 1,1,1,3,3,3-hexafluoroacetic acid, EtOAc = ethyl acetate.

The optimization of reaction conditions commenced with aminocyclization of tryptamine **1a** under previously reported conditions with $Rh_2(esp)_2$ as catalyst.[5c] Disappointingly, a messy reaction mixture was resulted, with desired product **3a** being isolated in 10% yield (Table 1, entry 2). In contrast, the reaction was totally retarded in the absence of catalyst (entry 1). Other rhodium catalysts were also screened and no improvement in yields was observed (entries 3-5). Furthermore, we also evaluated various transition metal complexes, which were ineffective for promoting the desired aminocyclization reaction (entries 6-11 and supporting information). Solvents played a crucial role in this reaction; when the reaction was run in aprotic solvents, low conversion and negligible yields were observed (entries 13-14). Although higher conversion was achieved by using protic solvents, only low isolated yields were obtained. After evaluating various protic solvents, MeOH provided a superior result, delivering amino-pyrroloindoline in 40% yield (entry 15). Reducing the reaction temperature to -20 °C was beneficial to the reaction, in which slightly improved yield was resulted (50%, entry 18). Eventually, full conversion of tryptamine **1a** with 57% isolated yield was achieved by adding $Rh_2(esp)_2$ and DPH in two portions (entry 19).

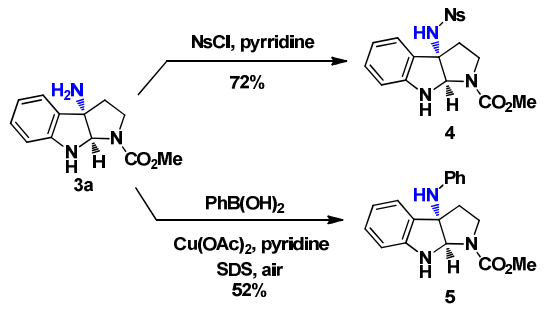
Table 2. Substrate scope[a,b]



[a] Reaction conditions: **1a** (0.1 mmol) in MeOH (1 mL) was added to a solution of DPH (0.08 mmol) and $Rh_2(esp)_2$ (1 mmol%) in MeOH (1 mL) at -20 °C. After 0.5 h, another mixture of DPH (0.08 mmol) and $Rh_2(esp)_2$ (1 mmol%) was added to the reaction mixture in one portion. [b] Isolated yields.

After identifying the optimized reaction conditions, examination of the substrate scope was implemented (Table 2). Typical electron-withdrawing protecting groups on nitrogen were compatible with the reaction conditions, providing amino-pyrroloindoline in moderate yields (**3a**-**3f**) and alkyl protecting

groups (e.g. Bn) only led to recovery of tryptamine. Next, substituents on indole ring were assessed. Various substituents on aromatic ring could be tolerated, affording the corresponding amino-pyrroloindoline in reasonable yields (**3g**-**3l**). The examples of bromine substituted tryptamine (**3h** and **3j**) were noteworthy, since they reserved the potential for further functionalization via cross-coupling reactions. Subjection of 2-substituted tryptamines to reaction conditions provided a facile construction of continuous quaternary carbon centers (**3m**-**3o**). Even substrate with an unsaturated ester moiety could be selectively cyclized to desired product albeit in low yields (**3o**, 23%). Other nucleophiles than carbamate were also investigated for this reaction. Imide and alcohol could also participate in the amino-cyclization reaction, leading to the corresponding heterocycles in acceptable yields (**3p** and **3q**). In the end, we found that tryptophan was smoothly converted to amino-pyrroloindoline in 58% combined yield with almost 1:1 diastereoselectivity (**3ra** and **3rb**),[8] which could be deliberately used for the synthesis of cyclotryptamine alkaloids (e.g. (+)-WIN 64821) according to Movassaghi's method.[2g,4o]



Scheme 1. Application of amino-pyrroloindoline **3a**. SDS = sodium dodecyl sulfate

Furthermore, the applications of amino-pyrroloindoline **3a** were investigated to demonstrate its synthetic utility (Scheme 1). The primary amine was more adjustable than the secondary aniline of **3a** since primary amine could be selectively protected with requisite groups, e.g. nosyl group to afford pyrroloindoline **4**. After slight modification of copper catalyzed Chan-Lam-Evans *N*-arylation reaction,[7] amino-pyrroloindoline **3a** was smoothly coupled with phenylboronic acid by catalytic $Cu(OAc)_2$ to afford pyrroloindoline **5**[9] in 52% yield in the presence of sodium dodecyl sulfate (SDS). The addition of SDS was critical for the reaction as low yields were obtained in the absence of SDS or in the presence of other additives (e.g. myristic acid[7d]).

In conclusion, a non-trivial aminocyclization of tryptamine and tryptophan with DPH catalyzed by $Rh_2(esp)_2$ was efficiently achieved. Various tryptamines and tryptophan were converted to naked amino-pyrroloindolines in useful yields by using this new protocol. The reaction provided a novel protocol for preparing naked amino-pyrroloindolines, which are key intermediates for the synthesis of cyclotryptamine alkaloids.

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Notes and references

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8 The relative configurations of **3ra** and **3rb** were established by NOE experiment (see supporting information).

9 Amino-pyrroloindoline **8** is a known compound, see ref. 3d.