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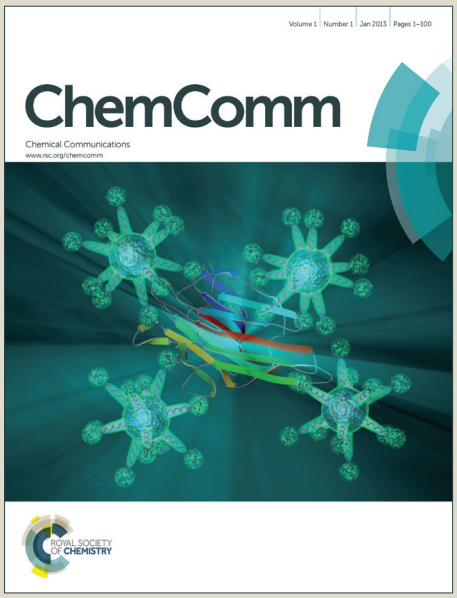

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An Efficient Synthesis of Pyrido[1,2-a]indoles through Aza-Nazarov Type Cyclization

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Transition metal free Brønsted acid mediated synthesis of biologically important pyrido[1,2-*a*]indole scaffolds through aza-Nazarov type cyclization of readily available diaryl(2-pyridyl)methanol using formic acid has been developed. This methodology has been successfully extended to synthesize atropisomers.

C-N bond formation is an important tool in organic synthesis for the synthesis of biologically and medicinally important nitrogen containing heterocycles in single step manner from readily available precursor.[1,2] In addition, intramolecular C–N bond formation is an efficient process to synthesize polycyclic amines in single step which is difficult by traditional synthetic methods.[3] Functionalities such as azides,[4] amides[5] and amines[6] are used as amine source for C-N bond formation. Due to readily available nature and stability, utilizing pyridine nitrogen as amine source for intramolecular C-N bond formation attracted the chemist for the synthesis of biologically important nitrogen containing heterocycles.[7]

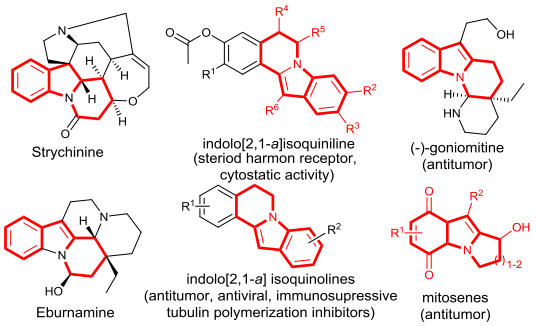
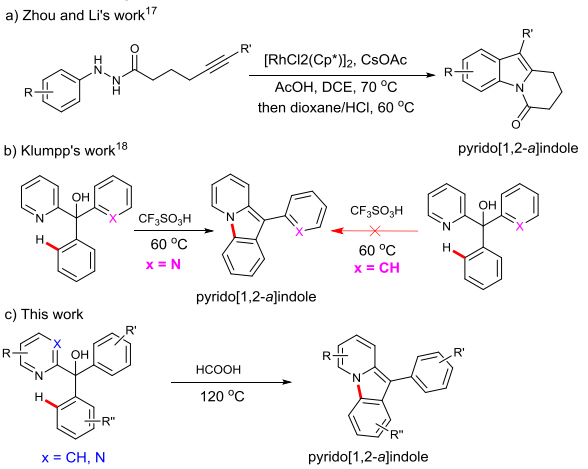


Fig 1. Some representative example for pyrido[1,2-*a*]indole containing biologically important molecules

Pyrido[1,2-*a*]indole, indolo[2,1-*a*]quinolone and pyrimido[1,2-*a*]indole are nitrogen containing heterocycles frequently found in several natural products (Figure 1). These molecules show broad range of biological activities such as anti-HIV,[8] anti-inflammatory,[9] 5-HT3 receptor antagonist,[10] H3 receptor antagonist,[11] usage as molecular probes such as cytostatic,[12] immunosuppressive,[13] tubulin polymerization inhibiting activities[14] and conductivity nature in material chemistry.[15]



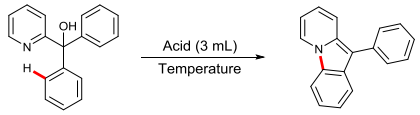
Scheme 1. Intramolecular C-N forming reaction for the synthesis of pyrido[1,2-*a*]indoles.

By owing their biological important, the synthesis of these class of compounds have been reported in the literature using transition metal catalyst.[16] Recently, Zhou *et al*. reported rhodium catalyzed C-H activation of alkyne-tethered arylhydrazines for the synthesis of pyrido[1,2-*a*]indoles (Scheme 1a).[17] In 2011, Klumpp *et al*. demonstrated metal free synthesis of pyrido[1,2-*a*]indoles from two heterocycle containing triaryl carbinol using triflic acid (CF_3SO_3H) (Scheme 1b).[18] However, when single heterocycle containing triaryl carbinol was subjected to this reaction condition, the starting material got decomposed.[18] To our continues effects towards important nitrogen containing heterocycles synthesis,[19] herein we

report metal free efficient synthesis of pyrido[1,2-*a*]indoles using formic acid from readily available triaryl methanol in single step (Scheme 1c). In this aza-Nazarov type cyclization process, pyridine nitrogen of triaryl methanol is acting as nitrogen source to give pyrido[1,2-*a*]indoles through aza-Nazarov type cyclization.

Diphenyl(pyridin-2-yl)methanol **1a** was chosen as model substrate for this cyclization reaction and formic acid (3 mL) as solvent as well as Brønsted acid source to achieve aza-Nazarov type cyclization and the results are summarized in Table 1. Interestingly, this reaction gave 95% of cyclized product **2a** at 130 ^{o}C (entry 1). To investigate the effect of Brønsted acid, various Bronsted acids such as pivalic acid (PivOH), acetic acid (AcOH) and trifluroacetic acid (TFA) were used as acid source as well as solvent. Among them, only acetic acid mediated reaction gave 31% isolated yield of **2a** after 8 hours (entry 3). To improve the efficiency of this reaction, the reaction was further carried out in various temperatures and a maximum yield of 96% was isolated at 120 ^{o}C in 6 hours. Choosing this as optimized reaction conditions, the substrate scope for this reaction was explored and the results are summarized in Table 2.[20]

Table 1. Optimization for aza-Nazarov type cyclization



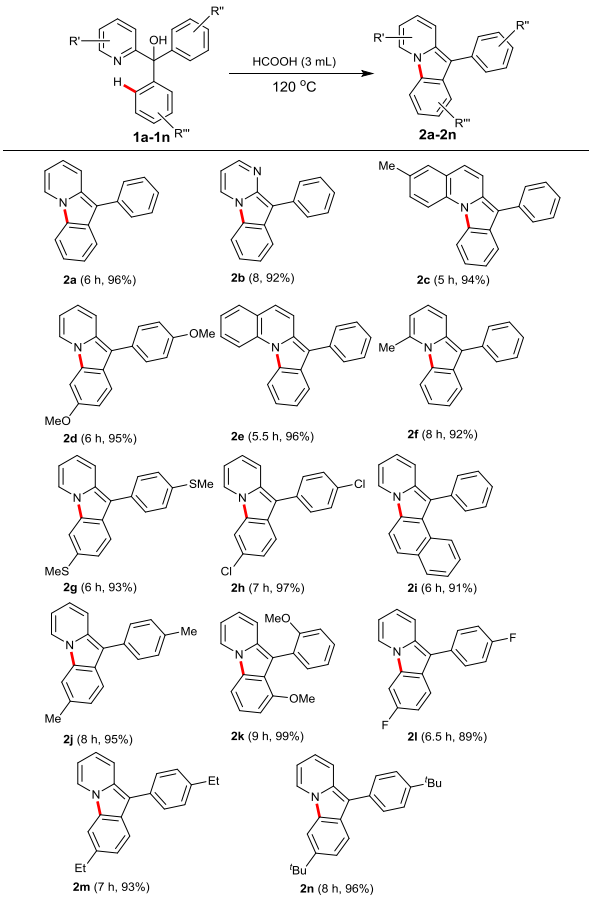
1a 2a

entry[a]	acid	temp. (^{o}C)	time (h)	yield (%)[b]
1	HCOOH	130	6	95
2	PivOH	130	24	-
3	AcOH	130	8	31
4	TFA	130	8	-
5	HCOOH	60	24	-
6	HCOOH	90	24	-
7	HCOOH	100	24	-[c]
8	HCOOH	110	24	36
9	**HCOOH**	**120**	**6**	**96**

[a] Reaction was performed with **1a** (1 mmol). [b] Isolated yield.
[c] 32% of triarylmethane was isolated

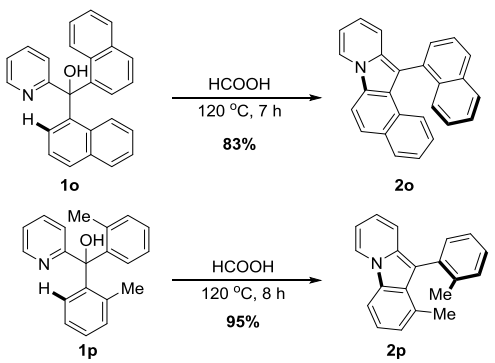
All the triarylmethanols having pyridine as well as quinoline moieties were successfully converted to corresponding cyclized product in good to excellent yields (Table 2). Substrates containing functional groups such as methoxy, chloro, thiomethyl, alkyl and fluoro in aromatic rings were well tolerated. Interestingly, pyrimidine containing triarylmethanol was also converted to corresponding aza-Nazarov type cyclized product **2b** in excellent yield under optimized reaction conditions (entry 2). Substitution on pyridine ring that is 6-methylpyridine containing triarylmethanol **1f** was successfully converted to corresponding intramolecular C−N bond formed product **2f** (entry 6). In addition, *p*-SMe **1g** and *p*-Cl **1h** group containing triaryl methanols were underwent smoothly and gave 93% and 97% of yield respectively (entries 7 and 8). Even, *p*-F **1l**, *p*-Et **1m** and *p*-*tert*-butyl **1n** containing triarylmethanols were also successfully converted to corresponding cyclized product with good to excellent yield (entries 11, 12 and 13).

When bulky group substituted starting materials such as two 1-naphthyl groups containing triarylmethanol **1o** and *o*-tolyl group containing triarylmethanol **1p** were converted to corresponding aza-Nazarov type cyclized products in excellent yields (Scheme 2). The naphthyl substituted aza-Nazarov type cyclized product **2o** was further confirmed by solid state X-ray analysis (Figure 2). Interestingly, both these molecules **2o** and **2p** have shown axial chirality**.** The chirality of **2o** and **2p** were further confirmed by high pressure liquid chromatography (HPLC) using chiral OD-H column[21] and HPLC chromatograms of these molecules are shown in Figure 3.[22] We strongly believe that the axial chirality of these important molecules will find prominent position in the field of medicinal chemistry.



[a] Isolated yield

Fig 2. Substrate scope for aza-Nazarov type cyclization reaction[a]



Scheme 2. Metal free synthesis of axial chiral molecules

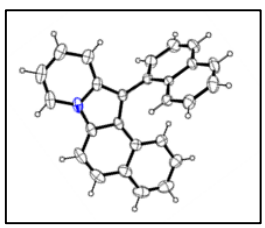


Figure 3. Single crystal X-ray structure of **2o** (CCDC No. 994568, 30% probability ellipsoid).

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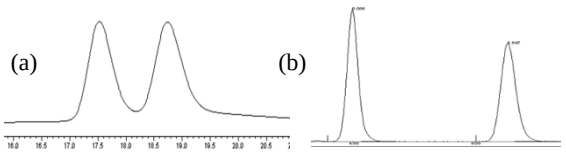
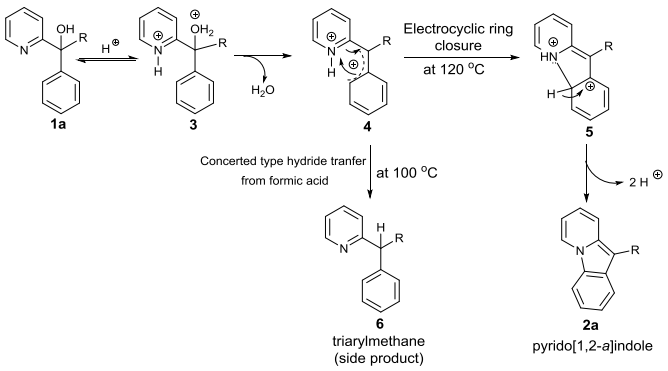


Figure 4. HPLC chromotogram of **2o** (a) and **2p** (b).



Scheme 3. Plausible reaction mechanism for the formic acid mediated aza-Nazarov type cyclization

Conclusions

In conclusion, formic acid mediated intramolecular azo-Nazarov cyclization reaction was developed for the synthesis of pyrido[1,2-*a*]indole derivatives. This methodology provides wide range of substrate scope such as pyridine, quinoline and pyrimidine containing triaryl methanol were successfully converted to corresponding aza-Nazarov type cyclized products in good to excellent yield. Under the optimized reaction conditions a wide range of functional groups such as thiomethyl, methoxy, chloro, fluoro etc. were well tolerated and all of them gave good to excellent yield. Very interestingly, axial chirality was found when substrate having bulky substitution at *ortho* position of the cyclized products.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental procedure for intramolecular C-H amination and tertiary alcohol formation reaction and copy of 1H NMR and 13C NMR spectra were given in SI. This material is available free of charge via the Internet at http://pubs.acs.org.. See DOI: 10.1039/c000000x/

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20 Diarylalkylmethanols such as methyl, *iso*-propyl and *tert*-butyl containing substrates did not undergo for aza-Nazarov type cyclization and unsymmetrical triarylmethanols gave mixture of cyclized product.

21 Determined using chiral OD-H column, 0.5 mL/min, 3 % IPA:hexanes for compound **2n** and chiral OD-H column 0.5 mL/min, 2 % IPA:hexanes for compound **2o**.

22 When we tried to resolve compound **2k** by HPLC using chiral columns (totally 9 columns were used), this compound **2k** did not resolve by any chiral column. So we are assuming that the compound **2k** may not be chiral compound.