Direct Synthesis of Structurally Divergent Indole Alkaloids from Simple Chemicals

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Abstract A direct and structurally divergent synthesis of indole alkaloids from very simple 2-vinylanilines, alkynes and TBN via a novel substrate fragmentation/cycloaddition strategy has been developed, which provides an efficient noble-metal-free approach to access a library of highly valuable indole derivatives of tryptamines and tryptamine-related oximes, lactams, and lactones, as well as β-carbolines, spiroindolines, and hexa-hydropyrrolo[2,3-*b*]indoles.

Keywords C-C bond cleavage, molecular diversity, indole alkaloids, trypthamines, radicals

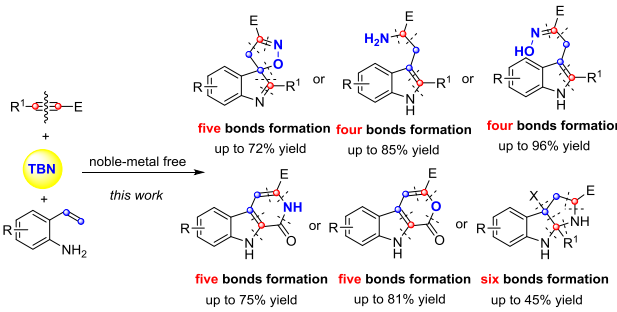
Introduction

Construction of chemical bond is the core issue of synthetic chemistry.[1] Employing the strategy of bond cleavage and reassembly, chemists would have a chance to synthesize more complex compounds from very simple starting materials in a highly efficient manner. This is undoubtedly very attractive, but it is very challenging because the complicated fragmentation of the substrates via C-C bond cleavage[2-3] and selective reassembly must be precisely controlled.

As a ubiquitous and key structural motif in nature, indoles are the structural cores in natural products and drugs[4], including tryptamine (Tryp) derivatives such as psilocin, psilocybin, and triptans; β-carbolines such as marinacarbolin A-D, Flazin and Flazinamide; spirooxindoles such as horsfiline and coerulescine; hexahydropyrrolo[2,3-*b*]indoles such as (-)-psychotriasine[4]. The preparation of divergent indole alkaloids is therefore an important strategy in drug discovery and development. However, most of the current synthetic strategies for accessing indole alkaloids suffer from limitations such as noble-metal catalysis, starting from indole complex substrates, and multiple synthetic steps. Moreover, in most cases, only one carbon skeleton was constructed by former methods. It has been shown that the collection synthesis[5] are powerful strategies to prepare structurally diverse compounds[6] from a common molecular scaffold. However, so far, direct access to structurally divergent indole alkaloids from readily available chemicals has not been achieved.

Encouraged by our studies of C≡C triple bond cleavage,[7] we hypothesized that trypthamines and related indole alkaloids could be synthesized from simple and readily available alkynes and an appropriate nitrogen source (Scheme 1). However, several challenges associated with this strategy should be addressed: 1) substrate fragmentation and reassembly is required to enable the formation of complex products; 2) the chemo-, regio- and stereo-selectivity should be precisely controlled; and 3) as many structurally divergent indole alkaloids as possible should be prepared by this strategy from the same simple precursors. Herein, we present a direct synthesis of structurally divergent indole alkaloids from simple three-component reaction via four or five bonds formation (Scheme 1).

Scheme 1. Structurally divergent synthesis of indole alkaloids



Experimental

We initially investigated the reactions of 2-vinylaniline **1a** and dimethyl acetylenedicarboxylate **2a** with different *N*-partners in HFIP. Unfortunately,

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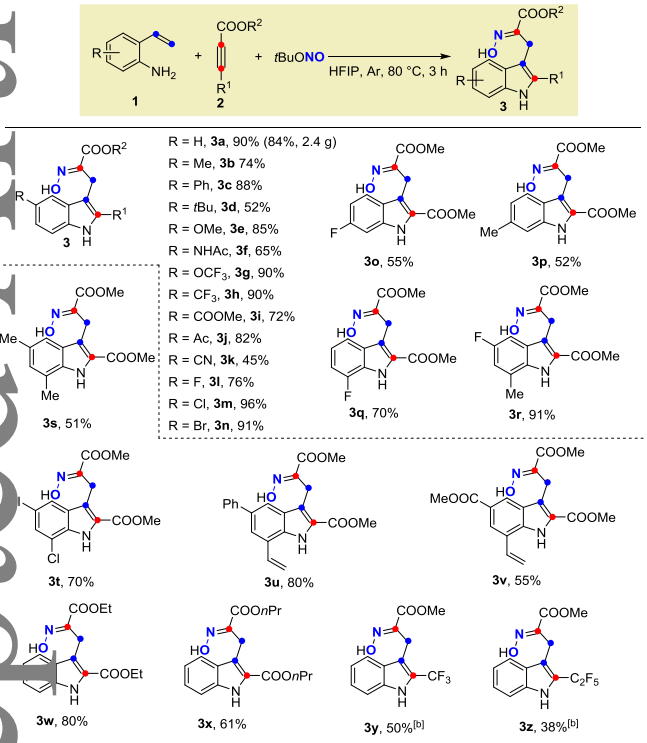
some common *N*-sources, such as $NaNO_2$, $AgNO_2$, $TMSN_3$, TsN_3, and BocNHOH did not provide the desired tryptamine derivative products (see SI). Interestingly, in the presence of *t*BuONO, which is widely employed in nitration reactions[8], the trypthamine-related oxime product **3a** was obtained in 90% yield (see SI). To our delight, by using a simple tandem reaction with zinc dust reduction, tryptamine derivatives **4a** could be obtained in 72% yield (**4a**). Thus, highly valuable tryptamine derivatives could be efficiently synthesized by this one-pot protocol.

Results and Discussion

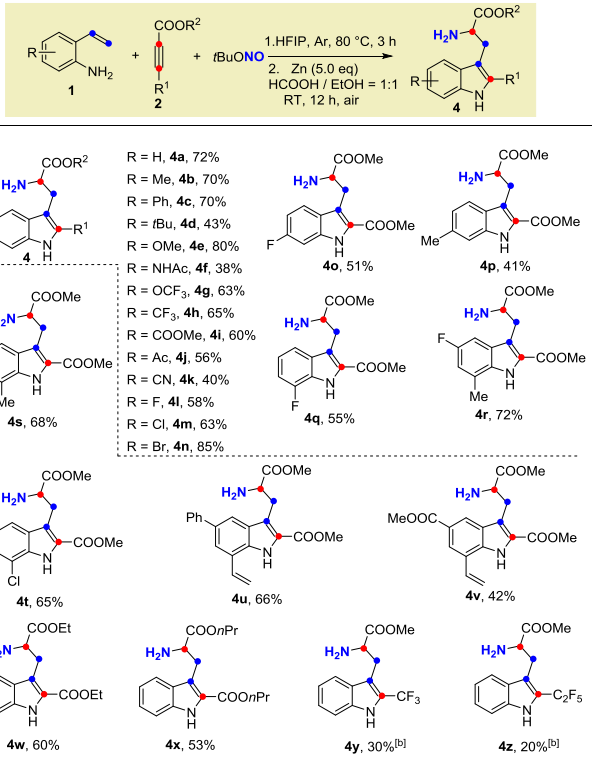
Scheme 2. The substrate scope of this transformation[a].



[a]**1** (0.24 mmol), **2** (0.24 mmol), *t*BuONO (0.2 mmol), HFIP (1.0 mL), stirred at 80 °C under Ar for 3 h. Isolated yields. [b]Stirred in mixed solvents (HFIP:DMSO = 1:1) at 120 °C under Ar for 24 h. Isolated yields.

With the optimied reaction conditions in hand (Table 1, entry 4), we subsequently investigated the substrate The scope of these two transformations was then investigated (Scheme 2 and 3). Various 2-vinylanilines **1** containing different functional groups were well tolerated and led to the desired tryptamine derivatives and corresponding oxime derivatives in good to excellent yields (Scheme 2 and 3). Notably, the reactions of unsymmetrical alkynes, such as the fluoroalkyl alkynes, also proceeded well and produced the corresponding products (**3y**-**3z** and **4y**-**4z**) with high regioselectivity. The gram scale reaction gave **3a** in 84% yield. Moreover, the structure of **3a** was confirmed by single-crystal X-ray crystallography (Fig. 1).

Scheme 3. Direct synthesis of tryptamine derivatives[a].



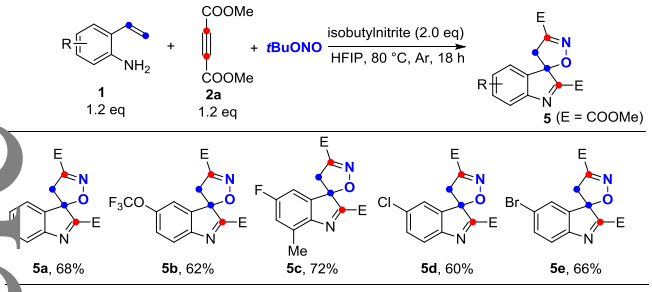
[a]**1** (0.24 mmol), **2** (0.24 mmol), *t*BuONO (0.2 mmol), HFIP (1.0 mL), stirred at 80 °C under Ar for 3 h, then Zn dust (5.0 eq), HCOOH (0.5 mL), EtOH (0.5 mL), stirr under air at RT for 12 h. Isolated yields. [b]Stirred in mixed solvents (HFIP:DMSO = 1:1) at 120 °C for 24 h, then step 2. Isolated yields.

We envisioned that this strategy might enable the preparation of a large number of structurally divergent indole alkaloids from the same simple precursors by tuning the reaction conditions via the tryptamine intermediates. Spiroindolines represent another important structural motif in many natural and bioactive compounds.[9] Interestingly, when two equivalents of isobutylnitrite was employed as the oxidant, the corresponding spiroindolines **5a** were obtained in good yield via the construction of five distinct chemical bonds (Scheme 4). However, using three equivalents of *t*BuONO directly gave low yield. A series of different substituents on the aromatic ring are compatible, to provide highly functionalized spiroindolines in moderate to good yields (**5b**-**e**). Moreover, the spiroindoline structure of **5a** was confirmed by single-crystal X-ray crystallography (Fig. 1).

It is worth noting that when $(OEt)_2P(=S)SH$ in 1,4-dioxane was added to the reaction mixture, β-carboline **6a** was obtained in 70% yield (Scheme 5). 1-Oxo-β-carbolines are also commonly found in natural products, pharmaceuticals, and bioactive compounds[10]. In addition, the motif is a useful building block and is frequently used in organic synthesis. Under these simple reaction conditions, various substituted β-carbolines were efficiently prepared (**6a-e**; Scheme 5). Therefore,

the current chemistry provides a practical and noble-metal free approach to β-carboline alkaloids *via* five distinct chemical bonds formation.

Scheme 4. Direct synthesis of spiroindoline derivatives.



Reaction conditions: **1** (0.24 mmol), **2a** (0.24 mmol), *t*BuONO (0.2 mmol), isobutylnitrite (0.4 mmol), HFIP (1.0 mL), stirred at 80 °C under Ar for 18 h. Isolated yields.

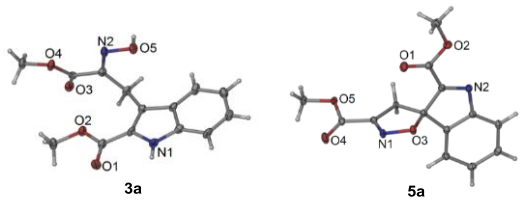
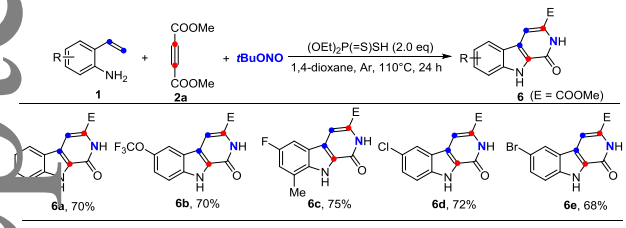


Figure 1. X-ray structure of **3a** and **5a**.

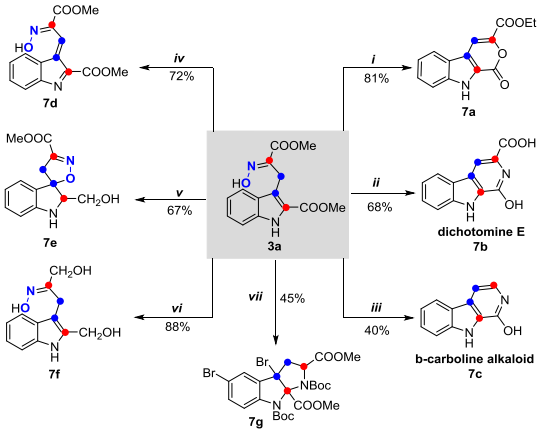
Scheme 5. Direct synthesis of β-carboline alkaloids derivatives.



Reaction conditions: **1** (0.24 mmol), **2a** (0.24 mmol), *t*BuONO (0.2 mmol), HFIP (1.0 mL), stirred at 80 °C under Ar for 3 h, then adding $(OEt)_2P(=S)SH$ (0.4 mmol), 1,4-dioxane (1 mL), stirred at 110 °C for 24 h. Isolated yields.

To further investigate the applications and efficiency of this strategy, we then evaluated the possibility of preparing more structurally divergent indole alkaloids through 1-2 derivatization steps from trypthamine oxime derivative **3** (Scheme 6). The hydrolysis of **3a** generated **7a** in 81% yield. Due to the unique structure of **3a**, direct intramolecular condensation and hydrolysis afforded natural β-carboline alkaloid dichotomine E (**7b**) in 68% yield, dichotomine E is a potent inhibitor of NO production[11]. To the best of our knowledge, the current method represents one of the shortest synthetic route to this compound. The biologically active β-carboline alkaloid **7c** could also be synthesized in 40% yield; this molecule can be isolated from the stems of *picrasma quassioides*[12]. Moreover, **3a** was oxidized to give **7d** in 72% yield. Spiroindoline derivative **7e** could be obtained in 67% yield by treating intermediate **5a** with $NaBH_4$/MeOH. Moreover, direct reduction of **3a** with $LiAlH_4$ gave **7f** in 88% yield. To our delight, the direct bromocyclization of tryptamine derivatives prepared from **3a** allows highly efficient synthesis of hexahydropyrrolo[2,3-*b*]indole core **7g**, which are present in diverse biologically active indole alkaloids such as (−)-psychotriasine and (−)-acetylardeemin[13]. Thus, the presented methodology could be a complimentary tool to access a library of useful tryptamines and tryptamine related oximes, lactams, and lactones as well as β-carbolines, spiroindolines, and hexahydropyrrolo[2,3-*b*]indoles.

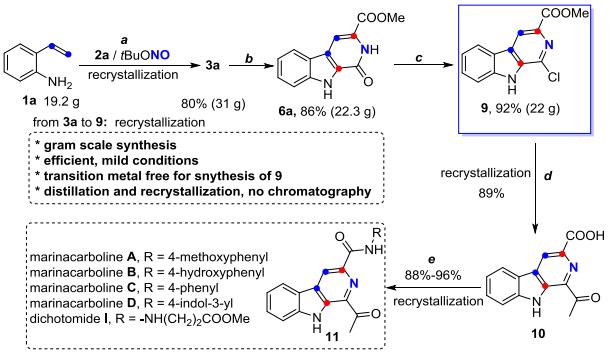
Scheme 6. Further application of this transformation. For detail conditions, see SI.



[a]Reaction conditions: ***i***, 6 M HCl (aq), EtOH, 80 °C; ***ii***, $(OEt)_2P(=S)SH$, 1,4-dioxane, 110 °C, then NaOH (aq), MeOH, RT; ***iii***, Zn, HCOOH, EtOH, RT, then KOH, MeOH, reflux, then $AgNO_3$, $Cu(OAc)_2$, MeCN, H_2O, 80 °C; ***iv***, oxone, $NaHCO_3$ (aq), acetone, 0 °C; ***v***, isobutylnitrite, HFIP, 80 °C, then $NaBH_4$, MeOH, 0 °C; ***vi***, $LiAlH_4$, THF, 0 °C; ***g***, Zn, HCOOH, EtOH, RT, then NaOH, $(Boc)_2O$, DCM, RT, then *N*-Bromosaccharin, PPTS, DCM, RT.

Then, we applied the current method to the total syntheis of natrual products (Scheme 7). 1,3-Disubstituted-β-carboline alkaloids marinacarbolines A-D were recently isolated from the fermentation broth of the actinomycete *Marinactinospora thermotolerans* SCSIO 00652, belonging to the family of *Nocardiopasaceae*[14]. These alkaloids exhibit antiplasmodial activities against Plasmodium falciparum lines 3D7 and Dd2. In 2013, Hibino and co-workers reported the first total synthesis of marinacarbolines A-D in ten steps[15]. To our delight, the marinacarbolines A-D could be efficiently synthesized only in 5 steps on a gram scale in 50-54% overall yields using the present method as the key step (Scheme 7). Notably, for the synthesis of key intermediate **9**, the whole process is transition-metal free and efficient under mild conditions. It it worth noting that all the purification steps rely on distillation and recrystallization, and no chromatography was required. To the best of our knowledge, the protocol reported herein is one of the most efficient and simplest methods for the synthesis of β-carboline derivatives and the related natural products marinacarbolines A-D.

Scheme 7. Further application of this protocol in the total synthesis of natural products.



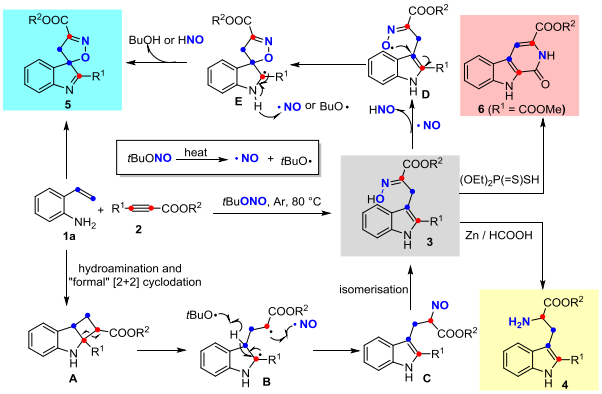
Reagents and conditions: **1a** was prepared from 2-aminophenethanol (**8**) with KOH by distillation in 88% yield (19.2 g) (see SI). ***a***, **1a**, **2a**, *t*BuONO, HFIP, 80 °C; ***b***, **3a**, $(OEt)_2P(=S)SH$, 1,4-dioxane, 110 °C; ***c***, **6a**, $POCl_3$, reflux; ***d***, 9, tributyl(1-ethoxyvinyl)tin, $PdCl_2(PPh_3)_2$, Et_4NCl, DMF, 100 °C; ***e***, 10, RNH_2, diethyl cyanophosphonate, Et_3N, DMF, RT.

According to the mechanistic studies (see SI), the mechanism is proposed in Scheme 8. The generated cyclobutane intermediate **A**[16] is unstable and easily undergoes C-C bond homolytic cleavage leading to form a di-radical intermediate **B**. Subsequently, the formed NO radical and *t*BuO radical from TBN synergisticly react with the di-radical **B** to finally afford the tryptamine derivative oxime **3**. With excess *t*BuONO or tBuONO, oxime products **3** could be further oxidized by NO radical to generate oxygen radical intermediate **D**. Then radical addition of the oxygen radical to double bond of **D** occurs to give a new radical intermediate E, following by H radical abstract by NO or BuO radical leading to the spiroindoline products **5**. In addition, the tryptamine products **4** could be obtained from **3** under reduction of Zn/HCOOH conditions, and the direct condensation of **3** affords the β-carboline products **6**.

Conclusions

In summary, a noble-metal free divergent synthetic approach for accessing structurally divergent indole alkaloids, including tryptamines, tryptamine-related oximes, lactams, and lactones as well as β-carbolines, spiroindolines, and hexahydropyrrolo[2,3-*b*]indoles, has been developed with high efficiency and selectivity. The very simple and readily available starting materials, 2-vinylanilines, alkynes and TBN, were demonstrated to be appropriate synthons for the construction of complex compounds through the formation of 4-5 distinct bonds via this substrate fragmentation/cycloaddition strategy. This chemistry provides a practical protocol and shows great potential in biological applications as well as in drug discovery. We anticipate that this strategy could inspire the development of additional multicomponent reactions and open an avenue for further exploration and utilization of small synthons in synthesis through in situ synergistic fragmentation and reassembly.

Scheme 8. Proposed mechanism for synthesis of structurally divergent indole alkaloids.



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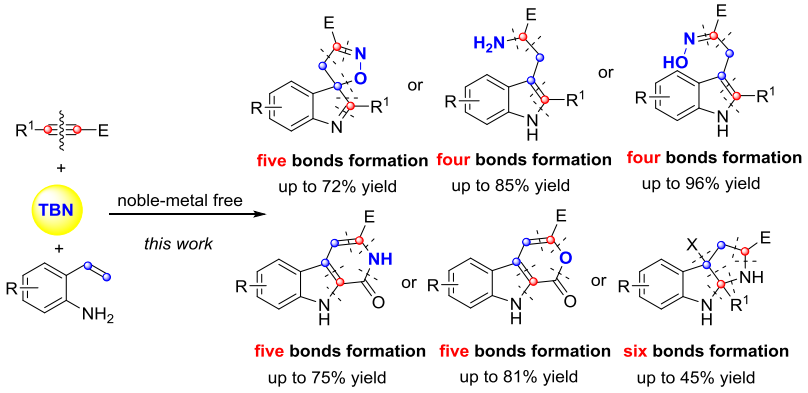

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