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tert-Butyl Nitrite (TBN) as the *N* atom source for the Synthesis of Substituted Cinnolines with 2-Vinylanilines and Relevant Mechanism was Studied

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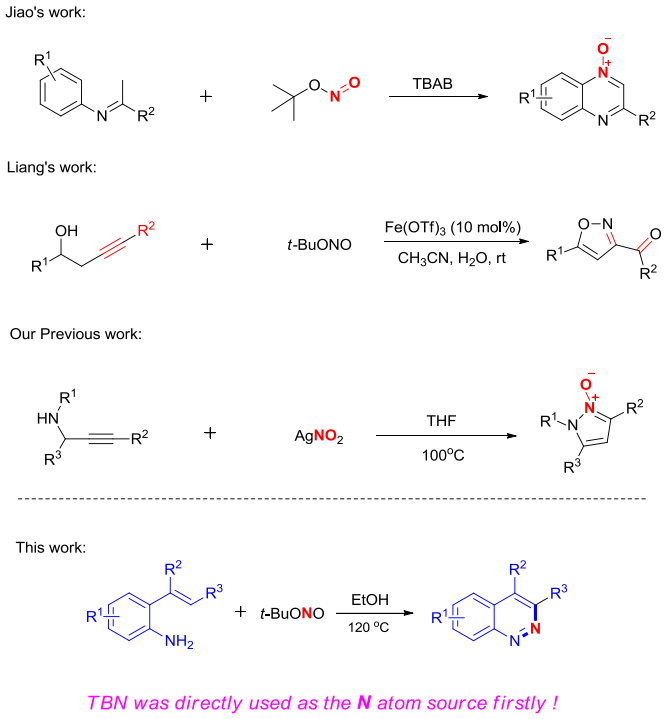
A green method to synthesize cinnolines by 6π electrocyclic reaction with alkenyl amines and TBN has been developed. TBN plays a dual role both as the nitrogen atom source and oxidant in this procedure. Relevant mechanism experiments reveal the reaction proceeds through electrocyclic reaction and with diazo hydroxide as a key intermediate.

Substituted cinnolines are important and versatile *N*-heterocycles. These compounds have received considerable interest owing to their anticancer, fungicidal and anti-inflammatory activities, as well as luminescent and optical properties.[1] The substituted cinnolines are conventionally synthesized by three well-described approaches with arenediazonium salt, arylhydrazone, and arylhydrazine as precursors.[2] Particular examples are the Widman-Stoermer reaction and Borsche-Herbert reaction, of which cinnolines are synthesized from the cyclization of phenyldiazonium ion with substituted *ortho*-alkynes and *ortho*-aminoacetophenones.[3] These strategies, however, rely on the use of well-defined substrates with N=N bond pre-introduced, suffering from harsh conditions and unsafe operations. In 2016, the Wu's group reported a straightforward strategy for the preparation of cinnolines *via* multicomponent coupling cyclization of arynes, tosylhydrazines, and α-bromo ketones.[4] One of practical strategies to overcome these limitations is to develop the direct intermolecular cyclization reaction from simple nitrogen-introducing substrates.

The development of new method for the utilization of *tert*-butyl nitrite (TBN) has been a hot research topic in recent years. Besides being used as an inexpensive, mild and readily accessible oxidant, TBN is also a reliable source of NO and NO_2 radicals. So the research in this area has been rapidly developed recently.[5] In this context, the synthesis of quinoxaline *N*-oxides have been developed by Jiao's group with TBN as a NO source (Scheme 1).[6] The Liang and co-workers reported an iron-catalyzed method for the synthesis of disubstituted isoxazoles from homopropargylic alcohol, TBN and H_2O (Scheme 1).[7] In contrast to these research and traditional *N* sources,[8] the utilization of TBN as a *N* source has been rarely exploited for the construction of *N*-heterocycles.[9] Thus, the development of efficient methods for the synthesis of heterocyclic compounds by employing TBN as *N* source following the principles of green chemistry is highly desirable.



Scheme 1. Typical reactions for TBN and $AgNO_2$

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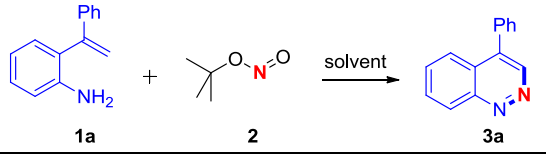
Table 1. Optimization of reaction conditions [a]



1a 2 3a

Entry	Solvent	Yield(%)[b]
1	$MeNO_2$	80
2	THF	50
3	1,4-diox	62
4	DMF	70
5	DMSO	74
6	NMP	59
7	PhMe	41
8	**EtOH**	**87**
9[c]	EtOH	77
10[d]	EtOH	56

[a] Reaction conditions: **1a** (0.3 mmol), TBN (0.6 mmol), solvent (2 mL), 120 °C. [b] Yields of isolated products. [c] 100 °C. [d] 80 °C. Entry in bold highlights the optimized reaction conditions, and the reaction time was monitored by TLC.

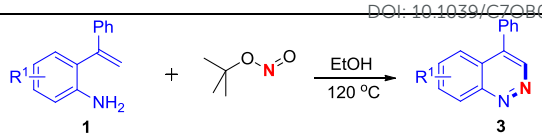
Inspired by our previous studies in dealing with the synthesis of heterocyclic compounds,[10] we reported here a [5+1] cyclization reaction for the synthesis of cinnolines with TBN as *N*1 unit. The reaction proceeds efficiently in ethanol without using any catalyst and additive.

The reaction was initially investigated with 2-(1-phenylvinyl)aniline (**1a**) and TBN. The desired product 4-phenylcinnoline (**3a**) was obtained in 80% yield when the reaction proceeded in $MeNO_2$ at 120 °C after 5 h. Encouraged by this result, several strategies were performed to optimize the reaction conditions. We firstly evaluated the effect of solvents, and the reaction in ethanol proved to be the most efficient, giving **3a** in 87% yield (Table 1, entry 8). The screening of other reaction parameters such as reaction temperature, reaction atmosphere and reaction time did not give a better result. Thus the conditions in Table 1 of entry 8 were used as the standard conditions.

With the optimized reaction conditions in hand, the scope and generality of this reaction were investigated as illustrated in Table 2. 2-Vinylanilines with either electron-donating or withdrawing R^1 groups reacted smoothly with TBN, giving desired substituted cinnolines in high yields. Generally, the reaction was slightly affected by the nature of R^1 groups of 2-vinylanilines, excepting the reaction of halogenated substrates provided products **3m** and **3o** in moderate yields.

Based on the successful synthesis of cinnolines from 2-alkenyl anilines, more challenging substrates were then employed and the results are illustrated in Table 3. 2-Alkenyl anilines with different R^1 and R^2 substituents readily reacted with TBN, and generated the desired substituted cinnolines in moderate to good yields Pleasingly, 2-(1-phenylvinyl)naphthalen-1-amine **1u** and 2-(prop-1-en-2-yl)aniline **1w** were successfully tolerated in this reaction, providing **3u** and **3w** in satisfactory yields, respectively.

Table 2. Scope of 2-vinylanilines [a]



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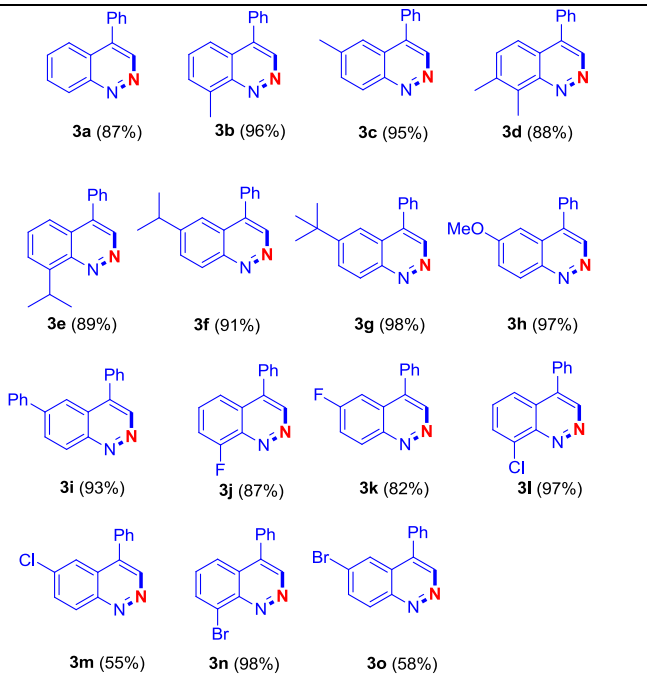
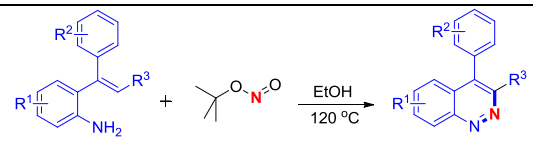


[a] Reaction conditions: **1** (0.3 mmol), TBN (0.6 mmol), EtOH (2 mL), 120 °C.

Table 3. The synthesis of substituted cinnolines [a]



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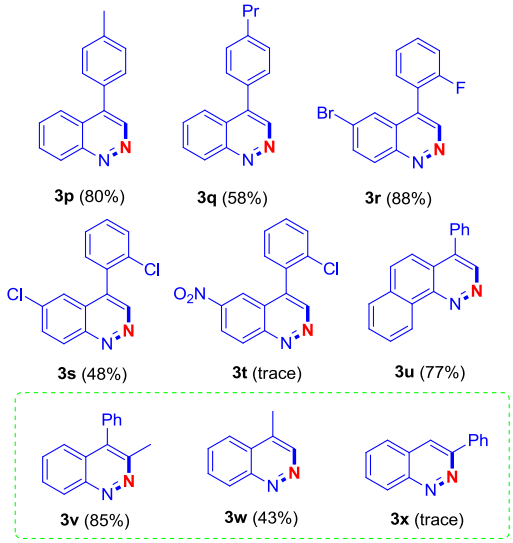
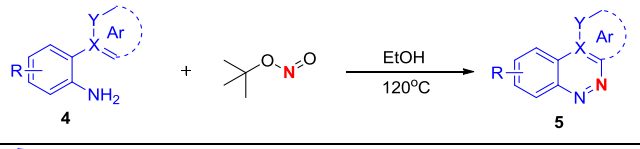
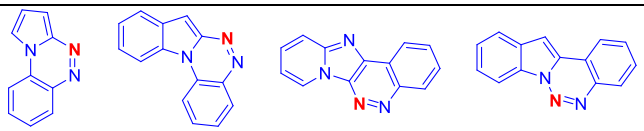


[a] Reaction conditions: **1** (0.3 mmol), TBN (0.6 mmol), EtOH (2 mL), 120 °C.

Table 4. The synthesis of substituted fused heterocyclic compounds [a]





5a, 83% **5b**, 92% **5c**, 55% **5d**, 40%

[a] Reaction conditions: **4** (0.3 mmol), TBN (0.6 mmol), EtOH (2 mL), 120 °C.

However, when (*E*)-2-styrylaniline **1x** was employed under the optimized conditions, only traces of corresponding product was detected.

Based on the success of *ortho*-alkenyl anilines in this reaction and the similar reactivity in many kinds of C(sp^2)–H transformations, we further investigated the scope of the substituted heterocyclic compounds **4** as substrate (Table 4). Fortunately, anilines with several *ortho*-heteroarenes, such as, pyrrole (**4a**), indole (**4b**, **4d**) and pyrrolo[1,2-*a*]pyridine (**4c**), could generate the desired products in moderate to excellent yields (**5a**-**5d**) under optimized conditions.

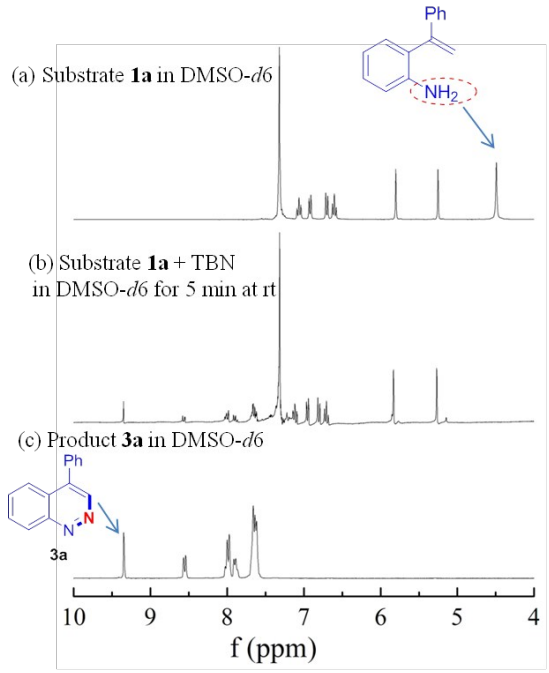
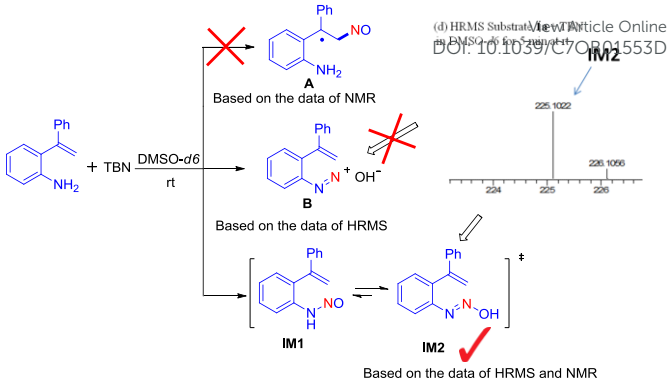


Figure 1. ^{1}H NMR analysis of this reaction

We next focused on elucidating the mechanism of this transformation. Firstly, *in situ* ^{1}H NMR (^{1}H Nuclear Magnetic Resonance) experiments were carried out to monitor the evolution of the groups during the process, and the selected



Scheme 2. The mechanism study of this reaction

spectra are listed in Figure 1. The experiment was performed with substrate **1a** and TBN in DMSO-d_6 at room temperature, since this reaction proceed rapidly under this conditions. When the reaction proceeded for 5 min, the signal of **1a** corresponding to the NH_2 protons disappeared. Meanwhile, the desired product **3a** was detected during the process. These results indicated that the reaction was occurred on the NH_2 group and ruled out the possibility of the addition of • NO and vinyl group of substrate **1a** (Scheme 2). Secondly, the HRMS (High Resolution Mass Spectrometry) measurement was also performed after the reaction of substrate **1a** with TBN in DMSO for 5 min. To our delight, a peak at m/z = 225.1022 corresponding to $C_{14}H_{13}N_2O$ $[M+H]^+$ was observed. This result was very important and it mean that the reaction did not undergo the pathway of cationic addition like Widman-Stoermer reaction. Based on the results of NMR and HRMS, the **IM2** should be the intermediate for this reaction (Scheme 2).

To further understand the mechanism of this reaction, control experiments were then performed. In the presence of TEMPO (2,2,6,6,-tetramethylpiperidyl-1-oxyl), substrate **1a** reacted smoothly and gave **3a** in 84% yield. The ESR (Electron-Spin Resonance) detection, combined with the use of a spin-trapping reagent such as MNP (2-methyl-2-nitrosopropane), were carried out. however, no useful radical intermediates and radical signals were obtained (see supporting information Scheme S1 and Figure S1). Moreover, the computational study of this reaction was further performed, and the results of Path **I** are summarized in Figure 2 (those of Path **II** are described in the Supporting Information). All the calculations were operated with the Gaussian09 suite of programs.[11] The reactants, transition states, intermediates and product were fully optimized at the M06-2X/6-31G(d, p) level of theory. The integral equation formalism polarized continuum model (IEFPCM) was applied to simulate the solvation effect of EtOH. The computational results displayed that the reactant **1a** interacts with **2** to lose one *tert*-butanol molecule *via* transition state **TS1** with an energy barrier of 29.41 kcal/mol. The intermediate **IM1** subsequently underwent intramolecular rearrangement to yield the intermediate **IM2** with an energy barrier of 30.44 kcal/mol. In the third step, the ring-closing reaction of **IM2** gave an intermediate **IM3** with the energy

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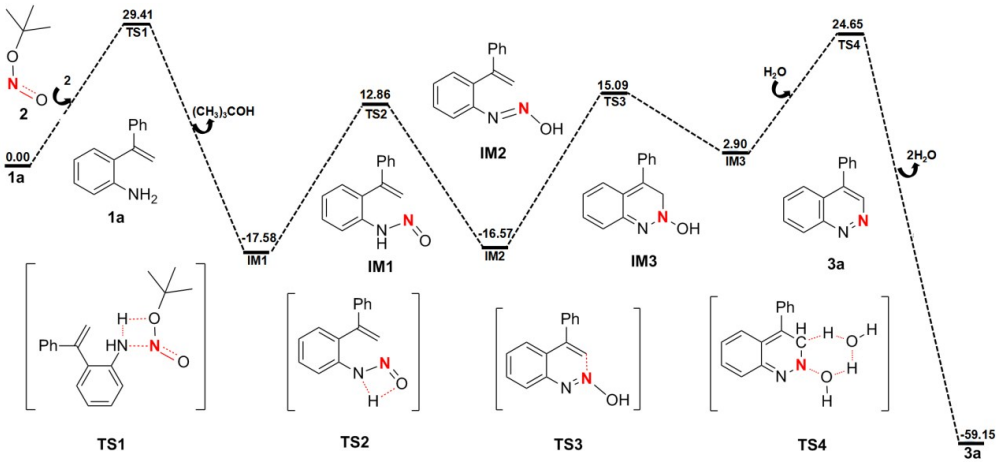
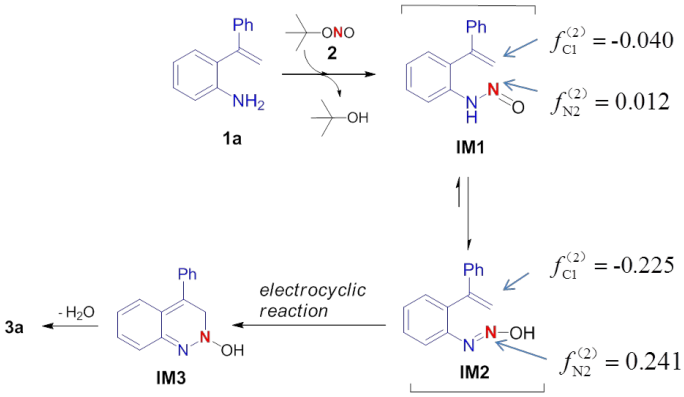


Figure 2. The total potential energy surface for the conversion from substrates **1a** and **2** to product **3a**

barrier of 31.66 kcal/mol . Finally, with the assistance of one H_2O molecule, the intermediate **IM3** lost one H_2O molecule to produce the final product **3a** *via* transition state **TS4** with a 21.75 kcal/mol barrier energy. The potential energy surface revealed that the exothermal releasing of the overall reaction is about ca.59.15 kcal/mol.



Scheme 3. Proposed Mechanism

Based on above results, a possible mechanism is proposed in Scheme 3. The nitro radical might be firstly generated through the decomposition of TBN. The reaction of substrate **1a** with nitro radical will produce an intermediate **IM1**,[12] which will equilibrate to intermediate **IM2**. The Fukui function can be used to predict the activity of atoms. The computational results show that the value of C1 and N2 atoms decreased from $f_{C1}^{(2)} = -0.225$ and $f_{N2}^{(2)} = 0.241$ (intermediate **IM2)** to $f_{C1}^{(2)} = -0.040$ and $f_{N2}^{(2)} = 0.012$ (intermediate **IM1)**, indicating that the electrocyclic reaction of **IM2** is much easier than that of **IM1** (Scheme 2). Subsequent cyclization of intermediate **IM2** gives the intermediate **IM3** *via* 6π electrocyclic reaction. Finally, the desired product **3a** is formed through dehydration process.

Conclusions

In conclusion, we have developed a green method to synthesize substituted cinnolines from 2-vinylanilines and TBN *via* tandem oxidation/cyclization reactions. During the synthesis of cinnolines, TBN acts as a dual role both as the *N* source and an oxidant. 2-Vinylanilines with different functional groups proceed well in this reaction and the desired cinnolines are obtained in moderate to good yields. The mechanism study reveals that the IM2 should be the intermediate and the reaction proceeds through 6π electrocyclization.

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