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Advanced Synthesis & Catalysis

Very Important Publication

Synthesis of Terminal *N*-Vinylazoles from Aromatic Aldehydes, DMSO, and Azoles Based DMSO as Terminal Carbon Synthon

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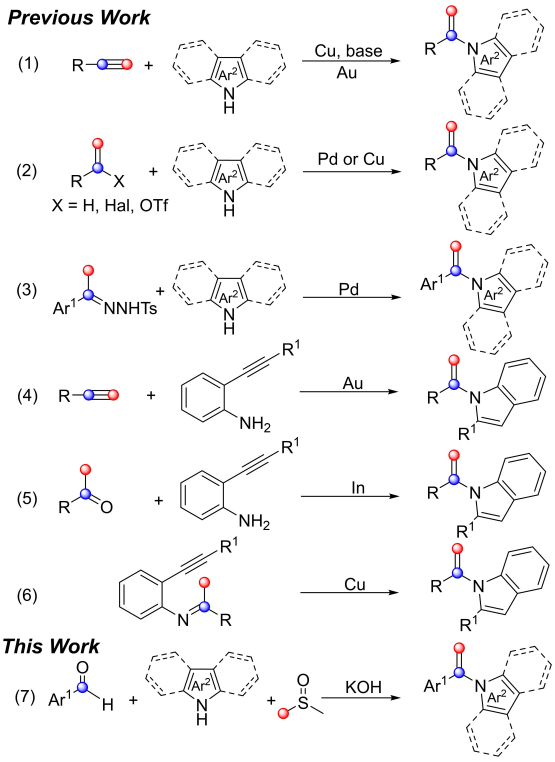
Abstract: A protocol for the synthesis of terminal *N*-vinylazoles from aromatic aldehydes, DMSO, and azoles has been reported. In this strategy, DMSO was involved in the construction of the C=C bond as a terminal carbon synthon. Both aromatic aldehydes and azoles could be well tolerated and give the corresponding terminal *N*-vinylazoles in 52–91% yields. Based on preliminary experiments, a plausible mechanism is proposed.

Keywords: Terminal *N*-vinylazoles; Aromatic Aldehydes; DMSO; Azoles; C=C and C–N bonds Formation

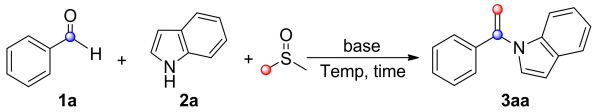
Introduction

Synthesis of terminal *N*-vinylazoles has attracted considerable attention of the organic chemists because the terminal *N*-vinylazole units widely existed in natural products, pharmaceuticals, and agrochemicals.[1] Futhermore, the terminal *N*-vinylazoles are also vital important intermediates in synthetic chemistry[2] and materials science.[3] In the past few decades, scientists have developed many strategies for the synthesis of the terminal *N*-vinylazoles. In general, the intermolecular coupling or the intramolecular annulation is used to prepare of terminal *N*-vinylazoles. Among these methods, the hydroamination of alkynes is the most straight forward approach for synthesizing terminal *N*-vinylazole.[4] For example, the Koenigs group described an Au(I)-catalyzed hydroamination reaction of terminal alkynes with carbazoles to furnish valuable terminal *N*-vinylcarbazoles (Scheme 1, Eqn. 1).[4b] With the development of transition metal-catalyzed reactions, Pd or Cu-catalyzed cross coupling of azoles with olefin and its derivatives for preparation of terminal *N*-vinylazoles has been well-studied.[5] In 2009, Xi and co-workers reported a methodology for the synthesis of terminal *N*-vinylazoles by CuI-catalyzed cross-coupling between azoles and α-bromostyrene (Scheme 1, Eqn. 2).[5h] Besides, Pd-catalyzed cross-coupling of *N*-tosylhydrazones with azoles to synthesize terminal *N*-vinylazoles has been reported by Cui and Alami group, respectively (Scheme 1, Eqn. 3).[6] These transition metal-catalyzed protocols are reliable and widely employed by many chemists, but most of these elegant works suffer from certain limitations. Such as troublesome operation, expensive catalysts/ligands especially raw materials requiring special structure. Recently, significant progress has been achieved in the synthesis of terminal *N*-vinylazoles *via* the cyclization reaction. For example, in 2007, Li group described a method to synthesize terminal *N*-vinylindoles *via* the intermolecular cyclization of o-alkynylanilines and alkynes (Scheme 1, Eqn. 4).[7] Afterward, Fujioka group accomplished a similar transformation through the intermolecular cyclization of ketones and *o*-alkynylanilines (Scheme 1, Eqn. 5).[8] Besides, Xu group reported a method for the synthesis of terminal *N*-vinylindoles *via* the intramolecular annulation of *N*-(2-alkynylphenyl) imine (Scheme 1, Eqn. 6).[9] However, these cycliza-



Scheme 1. Synthetic approaches toward terminal *N*-vinylazoles.

Table 1. Optimization of reaction conditions.[a]



Entry	Base	Time	Temp. (°C)	Yield (%)[b]
1	NaOH	30 min	80	18
2	\	30 min	80	0
3	K_2CO_3	30 min	80	trace
4	^{t}BuOK	30 min	80	78
5	**KOH**	**30 min**	**80**	**91**
6	KOH	20 min	80	75
7	KOH	40 min	80	91
8	KOH	30 min	70	69
9	KOH	30 min	90	82
10[c]	KOH	30 min	80	91
11[d]	KOH	30 min	80	31

[a] Reaction conditions: benzaldehyde (**1a**, 0.5 mmol), indole (**2a**, 1.0 mmol), base (2 mmol) and DMSO (2.5 mL).
[b] GC yield using 1,4-dichlorobenzene as an internal standard.
[c] Under O_2 atmosphere.
[d] Under Ar atmosphere.

tion strategies are just applicable to synthesis of terminal *N*-vinylindoles compounds. It is important to note that the C=C bond of the terminal *N*-vinylindoles in all of the above methods is derived from the single component, thus the raw materials requiring specific structures in these reactions.

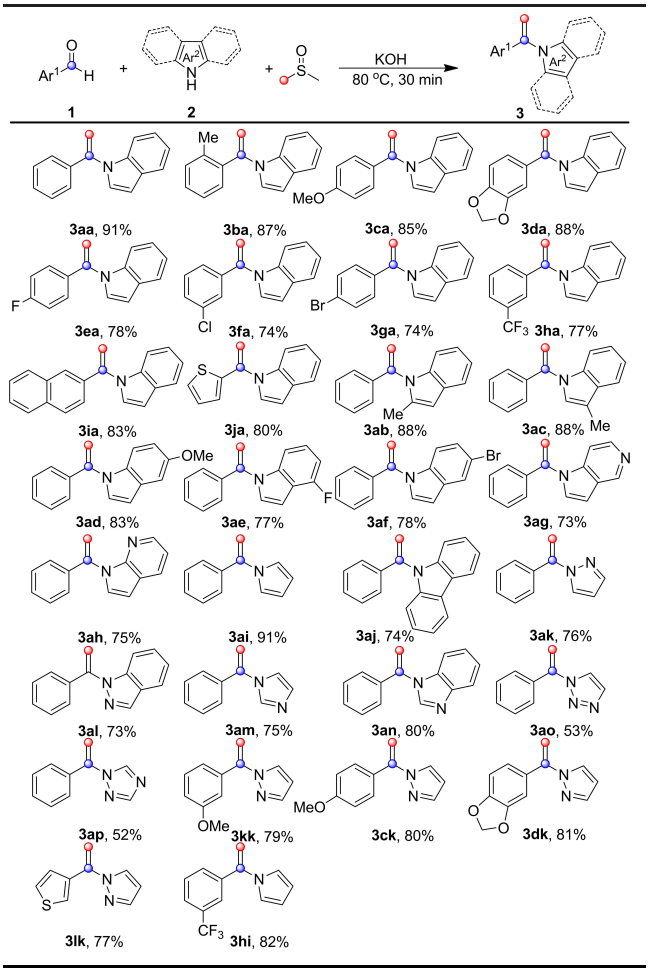
Dimethyl sulfoxide (DMSO) is a cheap, versatile solvent with low toxicity, great dissolving capacity, and relative stability, which is used widely in organic synthesis.[10] Moreover, DMSO as a carbon source for the construction of organic molecules has received much attention in recent years.[11] With our continued interest in DMSO as a carbon synthon,[12] we herein report a strategy for the synthesis of terminal *N*-vinylazoles *via* the three-component reaction of aromatic aldehydes, azoles, and DMSO (Scheme 1, Eqn. 7). In this strategy, DMSO was involved in the construction of the C=C bond as a terminal carbon synthon. To our best knowledge, this is the first example of the synthesis of terminal *N*-vinylazoles *via* the three-component reactions, and is also the first example for the construction of C=C bond *via* the dual-component reactions.

Results and Discussion

Initially, we explored benzaldehyde (**1a**) and indole (**2a**) as a model reactant and the results are summarized in Table 1. Heating reactants with DMSO at 80 °C for 30 min in the presence of NaOH afforded the desired **3aa** in 18% yield (Table 1, entry 1). Encouraged by this result, we investigated other reaction conditions, including the variation of base, time, and temperature. First, a series of inorganic base were screened and the results revealed that KOH was superior to other inorganic bases, such as NaOH, K_2CO_3 and ^{t}BuOK. In addition, the **3aa** could not be obtained under a base-free condition (Table 1, Entries 2–5). Subsequently, we carried out a series of tests on reaction time. The test results showed that the benzaldehyde was consumed when the reaction time was 30 minutes, and the yield was not improved by extending the reaction time (Table 1, Entries 6, 7). Furthermore, we screened the reaction temperature. Variation of the reaction temperature confirmed that 80 °C was the optimal condition for this protocol, with lower and higher temperatures affording decreased yields (Table 1, Entries 8, 9). Finally, the reactions have been performed in Ar and O_2 atmosphere, respectively (Table 1, Entries 10, 11). When reaction performed in O_2 atmosphere, the similar result was obtained in contrast to in air. With the Ar replacing of air, the yield of **3aa** decreased significantly, which indicated that O_2 in air played a certain role in the reaction.

Having established the optimized reaction conditions, the substrate scope of aldehydes was explored firstly and the results are summarized in Table 2. For

Table 2. The scope of aldehydes and azoles for preparation of terminal *N*-vinylazoles.[a,b]



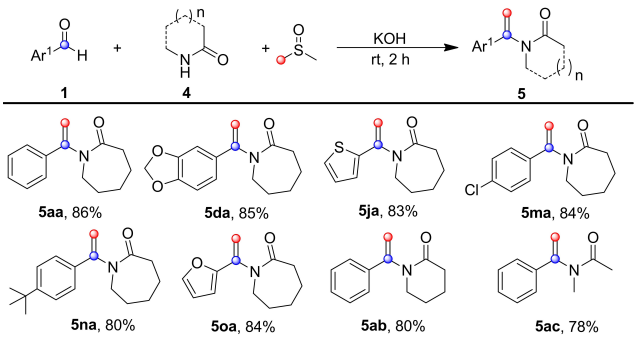
[a] Reaction conditions: aldehydes (**1**, 0.5 mmol), azoles (**2**, 1.0 mmol), KOH (2 mmol), DMSO (2.5 mL), at 80 °C for 30 min.
[b] Isolated yield.

example, aryl aldehydes bearing an electron-rich group (2-Me, 4-OMe, 3-OMe and 3,4-$(OMe)_2$) as well as an electron-deficient group (3-CF_3) all reacted smoothly, providing products **3 ba**–**3 da** and **3 ha** in moderate to good yields (77%–87%). An array of halogen substituents (4-F, 3-Cl, and 4-Br) were also compatible with the reaction to furnish products **3 ea**–**3 ga** in 74%–78% yields, therefore providing the possibility for synthetic derivatization. Gratifyingly, 2-naphthaldehyde also provided the *N*-vinylindole in 83% yield (**3 ia**). Furthermore, thiophene-2-carbaldehyde readily underwent the reaction to generate the expected product in high yield (**3 ja**). However, when aryl aldehydes were replaced by aliphatic aldehydes, the corresponding products could not be gained. Subsequently, the scope of the reaction was further explored using a variety of substituted indoles. For example, indoles bearing electron-rich group (2-Me, 3-Me and 5-OCH_3), and electron-deficient group (4-F and 5-Br) were tolerated, affording the corresponding products in moderate to good yields (**3 ab**–**3 af**). Delightfully, other azaindole substrates such as 5-azaindole and 7-azaindole also be employed to form the corresponding products without any difficulties (**3 ag**–**3 ah**). Encouraged by the results obtained with substituted indoles, we proceeded to apply this catalytic system to other azoles. To our delight, other azoles, such as pyrrole, carbazole, pyrazole, indazole, imidazole, benzimidazole, 1H-1,2,3-triazole, and 1H-1,2,4-triazole also produced the corresponding terminal *N*-vinylazoles products (**3 ai**–**3 hi**) with moderate to good yields, many of which are not readily accessible by conventional methods.

Enamides constitute the core structure of many functional materials[13] and natural products of biological significance.[14] Encouraged by the above results, we speculated that using amides instead of azoles could efficient synthesis of enamides by this strategy. Therefore, we tested the reaction of benzaldehyde with caprolactam by slightly modifying the reaction conditions. Fortunately, the reaction was proceeded smoothly at room temperature and the desired product **5 aa** was obtained with a yield of 86% (Table 3). Furthermore, other aromatic aldehydes and amides could also produce the corresponding enamides under the same conditions with good yields (**5 da**–**5 ac**). Besides, we also tried to use phthalimide as a substrate in this method. Unfortunately, the desired product was not detected.

More practically, a gram-scale reaction involving 10.0 mmol benzaldehyde, 15.0 mmol indole and 20.0 mmol KOH has also been conducted in this work. As a result, 76% yield of **3 aa** (1664.4 mg) was

Table 3. The scope of aldehydes and amides for preparation of enamides.[a,b]

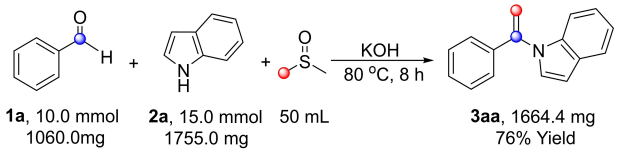


[a] Reaction conditions: aldehydes (**1**, 0.5 mmol), amides (**4**, 1.0 mmol) KOH (2 mmol), DMSO (2.5 mL), at room temperature for 2 h.
[b] Isolated yield.

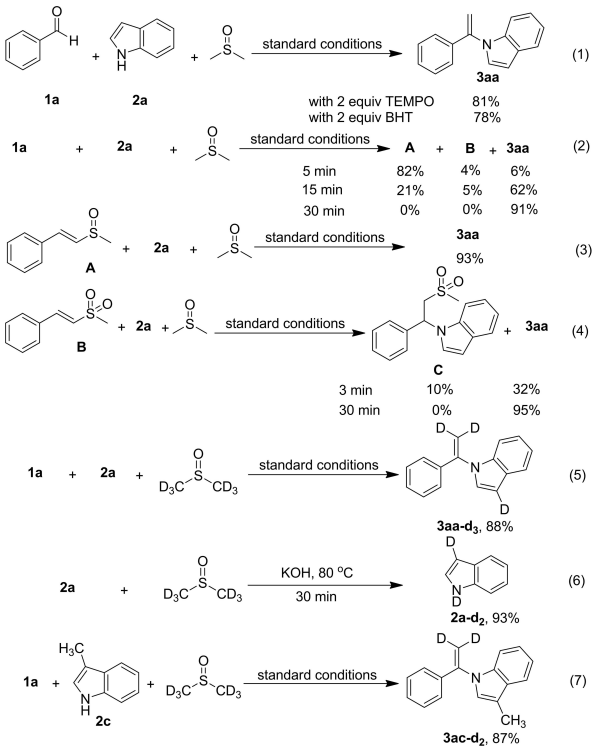
obtained using flash column chromatography on silica, that clearly showing its potential application in organic synthesis (Scheme 2).

To further understand the reaction mechanism, several control experiments were conducted (Scheme 3). By addition of 2 equiv. radical inhibitor TEMPO or BHT, product **3 aa** was still obtained in high yields under standard reaction conditions, indicating that this reaction may not proceed *via* a radical process (eq. 1). When the model reaction was stopped at 5 min, ca. 82% (methylsulfinyl)vinyl)benzene (**A**), 4% (*E*)-(2-(methylsulfonyl)vinyl)benzene (**B**) and 6% **3 aa** were detected by GC-MS. By further heating the reaction mixture to 15 min, ca. 21% **A**, 5% **B** and 62% **3 aa** were detected. When the model reaction was stopped at 30 min, **A** and **B** disappeared, whereas the yield of **3 aa** was increased to 91%, implying that **A** and **B** would be the key intermediates in this reaction (eq. 2). Pure **A** and **B** were synthesized following the established procedure. Under the standard reaction conditions, both **A** and **B** could be converted to **3 aa** in 93% and 95% yields, respectively (eq. 3 and 4). These results further proved that **A** and **B** would be the key intermediates in this reaction. Intermediate **B** was used to react with **2 a** under standard conditions, when the reaction stoped at 3 min, ca. 10% intermediate **C** and 32% **3 aa** were detected. When the reaction was stopped at 30 min, **C** disappeared, whereas the yield of **3 aa** was increased to 95%. The deuterium-experiments were also carried out. By using DMSO-d_6 instead, the partially deuterated product **3 aa-d$_3$** was isolated, which showing that DMSO was a source of methine units. In addition, there have hydrogen exchange reaction in the C3-H and N–H of indoles (eq. 5 and 6). Finally, our conclusion was confirmed by using 3-methylindole instead of indole (eq. 7).

On the basis of the above experimental results and in combination with previous literature,[15–18] a reasonable reaction mechanism was proposed using benzaldehyde **1 a** and indole **2 a** as an example and outlined in Scheme 4. Initially, benzaldehyde **1 a** reacted with DMSO under base conditions to give the styryl sulfoxide **A** through an aldol condensation reaction. In the presence of O_2, styryl sulfoxide **A** underwent oxidation to generate styryl sulfone **B**, followed by addition with indole **2 a** to form **C**. Subsequently, intermediate **C** by the base-assisted deprotonation yield an anion **D** with one molecule of water been released. Finally, the intermediate **D** underwent *β*-elimination to afford the final product **3 aa**.



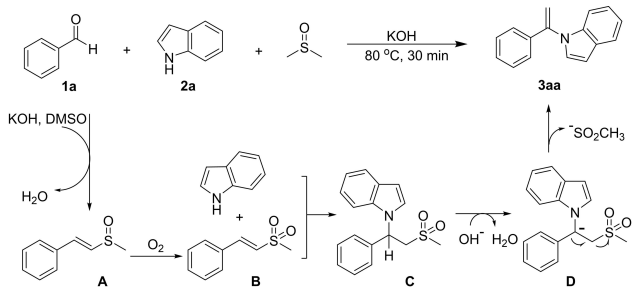
Scheme 2. Gram-scale reactions.



Scheme 3. Control experiments.

Conclusion

In summary, we have disclosed a three-component assembly reaction between aromatic aldehydes, DMSO, and azoles/amides. Various terminal *N*-vinylazoles and enamides were synthesized in good yields. What's more, this reaction could be conducted on a 10 mmol scale, clearly showing the potential practicality of this reaction in organic synthesis. On the basis of control experiments and literature precedents, a plausible reaction path accounting well for the single carbon transfer as well as C=C and C–N bond formations.



Scheme 4. Proposed mechanism.

Experimental Section

In a Schlenk tube of 25 mL, KOH (1.0 mmol, 56 mg), DMSO (2.5 mL), aldehydes (1, 0.5 mmol), azoles (2, 1.0 mmol) were added. The mixture was stirred at 80 °C for 30 min. After completion of the reaction, the resulting solution was cooled to room temperature; then it was diluted with ethyl acetate (6 mL), washed with water (6 mL), extracted with ethyl acetate (6 × 3 mL), and dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel to give the desired product final product.

Acknowledgements

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RESEARCH ARTICLE

Synthesis of Terminal *N*-Vinylazoles from Aromatic Aldehydes, DMSO, and Azoles Based DMSO as Terminal Carbon Synthon

Adv. Synth. Catal. **2021**, *363*, 1 – 7

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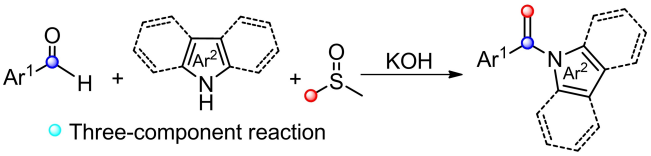

- Three-component reaction
- 30 examples with 52 - 91% yields
- C=C and C-N bonds Formation
- Construct C=C bond via dual-components