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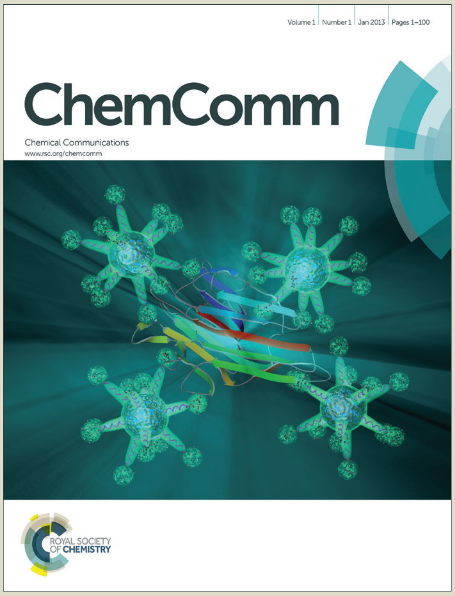

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I_2- catalyzed synthesis of substituted imidazoles from vinyl azides and benzylamines

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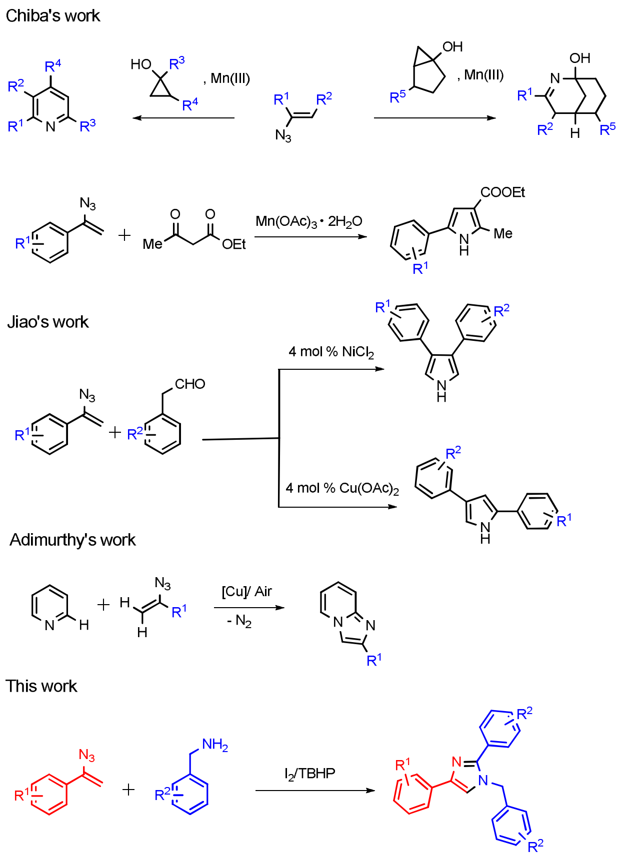
A novel and efficient I_2-catalyzed oxidative tandem cyclization of simple vinyl azides and benzylamines has been developed for the synthesis of substituted imidazoles. In this reaction, various substituted groups on vinyl azides and benzylamines proceed smoothly and the desired imidazoles are obtained in moderate to good yields.

Imidazoles and their derivatives are one of the important class of *N*-heterocycles broadly found in natural products[1] and pharmaceutical compounds[2]. The increasing importance of substituted imidazoles has spurred a vigorous research for the development of new synthetic methods. Great progress have been achieved for the synthesis of the imidazole scaffolds in the past years.[3] Various reaction systems, such as transition-metal catalyzed[4], Lewis acids[5] and base[6], are effective for the construction of imidazole structures[7]. However, novel and efficient synthetic routes to substituted imidazoles are of continuous interest. Especially, synthetic methods to simple substituted imidazoles with benzyl amines are still limited.[8]

Recently, vinyl azides, as attractive and challenging substrates, have drawn much attentions for their growing applications in the synthesis of *N*-heterocyclic compounds.[9] In the past several years, the excellent and significant works on construction of *N*-heterocycles with vinyl azides had been reported by the groups of Chiba[10] and Jiao[11] (Scheme 1). Recently, the group of Adimurthy had also reported a novel method for the synthesis of imidazo[1,2-*a*]pyridines with vinyl azides (Scheme 1).[12] To our knowledge, the new method for synthesis of substituted



Scheme 1. Vinyl azides in the synthesis of heterocycles

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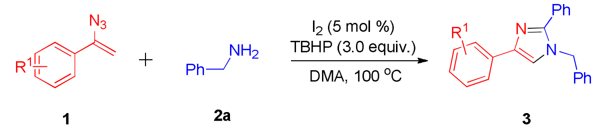
Table 1. The reaction of substituted vinyl azides and phenylmethanamine [a]



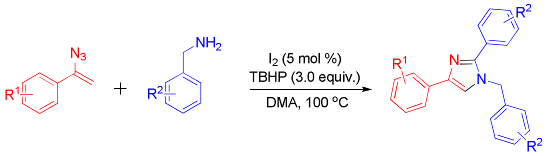
entry		R^1	product	yields(%)[b]
1	**1a**	H	**3aa**	76
2	**1b**	2-Me	**3ba**	51
3	**1c**	4-Me	**3ca**	72
4	**1d**	4-*t*Bu	**3da**	75
5	**1e**	2,5-*di*Me	**3ea**	33
6	**1f**	2-F	**3fa**	68
7	**1g**	2-Cl	**3ga**	74
8	**1h**	2-Br	**3ha**	57
9	**1i**	3-CI	**3ia**	79
10	**1j**	4-F	**3ja**	66
11	**1k**	4-Cl	**3ka**	56
12	**1l**	4-Br	**3la**	85

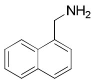
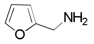
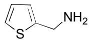
[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.5 mmol), I_2 (5 mol %), TBHP (3.0 equiv), DMA (2 mL), 100 °C, 10 h. [b] Yields of isolated products.

imidazoles with vinyl azides is still appreciated. Inspired by the works of utilization vinyl azides and our experiences in development of new and efficient methods for the construction heterocyclic compounds[13], herein, we report a novel and facial approach to substituted imidazoles from vinyl azides and benzylamines catalyzed by iodine.

Our study was initiated by treating (1-azidovinyl)benzene (**1a**) and phenylmethanamine (**2a**) with I_2 (2.2 equiv) in DMF at 100 °C for 6 h. We found that 1-benzyl-2,4-diphenyl-1*H*- imidazole (**3aa**) was obtained in 37% yield (See supporting information, Table S1, entry 1). The structure of **3aa** was confirmed by spectroscopic analysis and further confirmed by single crystal X-ray analysis (See supporting information, Figure 1). In order to improve the yield of this reaction, we then replaced the catalyst/oxidant systems to KI/TBHP, TBAI/TBHP and I_2/TBHP (Table S1, entries 2-5). As presented in Table S1, the reaction proceeded more efficiently in the systems of I_2/TBHP (Table S1, entry 5). This result promoted us to investigate other oxidants for

Table 2. The reaction of substituted vinyl azides and benzylamines[a]



entry		R^1		R^2	product	yields(%)[b]
1	**1a**	H	**2b**	2-Me	**3ab**	68
2	**1a**	H	**2c**	3-Me	**3ac**	73
3	**1a**	H	**2d**	4-Me	**3ad**	75
4	**1a**	H	**2e**	2-OMe	**3ae**	71
5	**1a**	H	**2f**	3-OMe	**3af**	56
6	**1a**	H	**2g**	4-OMe	**3ag**	81
7	**1a**	H	**2h**	2,4-*di*OMe	**3ah**	88
8	**1a**	H	**2i**	3,4-*di*OMe	**3ai**	42
9	**1a**	H	**2j**	3,5-*di*OMe	**3aj**	79
10	**1a**	H	**2k**	4-OH	**3ak**	-
11	**1a**	H	**2l**	2-F	**3al**	84
12	**1a**	H	**2m**	3-F	**3am**	68
13	**1a**	H	**2n**	4-F	**3an**	73
14	**1a**	H	**2o**	4-CI	**3ao**	81
15	**1a**	H	**2p**	4-Br	**3ap**	70
16	**1a**	H	**2q**	4-CF$_3$	**3aq**	72
17	**1a**	H	**2r**	2,4-*di*Cl	**3ar**	71
18	**1a**	H	**2s**	 NH$_2$	**3as**	87
19	**1a**	H	**2t**	 O NH$_2$	**3at**	79
20	**1a**	H	**2u**	 S NH$_2$	**3au**	42
21	**1a**	H	**2v**	*n*-octylamine	**3av**	-
22	**1c**	4-Me	**2b**	2-Me	**3cb**	77
23	**1c**	4-Me	**2f**	3-OMe	**3cf**	74
24	**1f**	2-F	**2b**	2-Me	**3fb**	50
25	**1f**	2-F	**2q**	2,4-*di*Cl	**3fq**	93

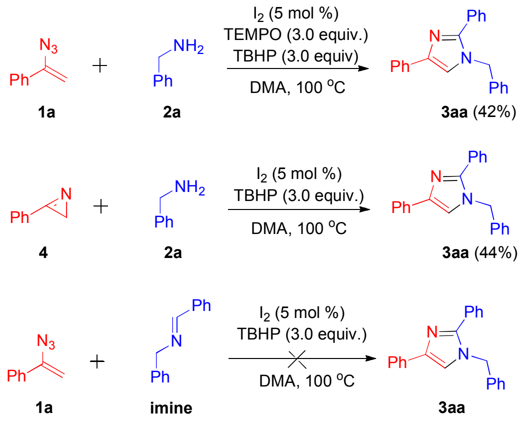
[a] Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), I_2 (5 mol %), TBHP (3.0 equiv), DMA (2 mL), 100 °C, 10 h. [b] Yields of isolated products.

the reaction, but no improvement was observed after examined (Table S1, entry 7-12). Notably, the reaction without I_2 can not generate the desired imidazole (Table S1, entry 6). Further optimization of solvents demonstrated that DMA was the optimized solvent for the formation of **3aa** (Table S1, entry 13).

The yields did not improve when HOAc or pyridine was added to the reaction. After screening other parameters such as reaction temperature and time, the optimized reaction system was established and showed in Table S1 as entry 13.

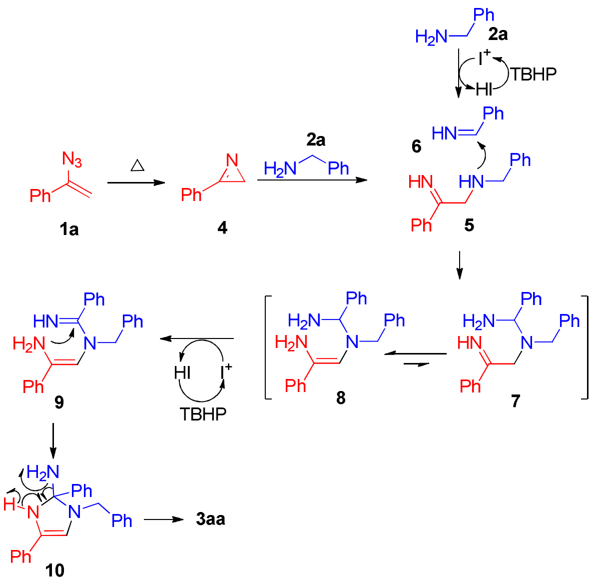
Having identified the optimized reaction conditions, the scope and generality of this reaction were investigated and the results were illustrated in Table 1. A series of vinyl azides with electron-donating or withdrawing groups could react with benzylamine smoothly in the reaction and the desired substituted imidazoles could be efficiently obtained in moderate yields. As shown in Table 1, the reaction was not significantly affected by the nature of the groups in aromatic ring of vinyl azides. The position of substituents on the benzene ring had a slight impact on the reaction yields.

Encouraged by these results, further experiments were conducted for the reaction of vinyl azides and substituted benzylamines under optimized conditions, and the results were shown in Table 2. A series of substituted imidazoles were obtained efficiently by this new approach. The electronic effects of substituents on the aromatic ring of benzylamines did not influence the reactivity and provided the desired imidazoles in moderate to good yields. However, the OH group on the aromatic ring of benzylamine can not give the desired product. The process was also extended to naphthalen-1-ylmethanamine **2s** and generated the desired product **3as** in 87% yield. Additionally, the furan-2-ylmethanamine **2t** and thiophen-2-ylmethanamine **2u** displayed better compatibility and gave the desired products **3at** and **3au** in 79% and 42% yields, respectively. Meanwhile, the *n*-octylamine **2v** was also employed for this reaction, but no desired product was obtained. Further investigation revealed that the substituted groups on the vinyl azides and benzylamines simultaneously also performed well in this process and provided the desired products efficiently.



Scheme 2. Control experiments

In order to obtain further insights into this reaction, several control experiments were investigated (Scheme 2). Firstly, the reaction of **1a** and **2a** were conducted in the presence of 3.0 equiv. of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy)under optimized conditions, only 42% yield of **3aa** was obtained. Furthermore, the substrate **2a** was employed to react with 3-phenyl-2*H*-azirine **4** to probe the reaction and the desired product **3aa** was isolated in 44% yield. Those above results reveal that the compound **4** should be the intermediate of the transformation and the reaction may undergo the radical pathway in the process. Moreover, when the substrate **1a** and imine were subjected to the standard conditions, no desired product was detected.



Scheme 3. Proposed mechanism

On the basis of the above results, a proposed mechanism for this transformation is illustrated in Scheme 3. Initially, the substrate **1a** is converted to 2*H*-azirine **4** with thermal decomposition. Then, a nucleophilic attack may occur between the substrate **2a** and **4** to produce the intermediate **5**.[10a,10c,11,12,14] Subsequently, **5** attacks the imine **6**, which is generated by oxidation of **2a**, to provide the intermediate **7**. The **7** equilibrates to intermediate **8** under optimized conditions. The compound **9**, which is generated by oxidation of **8**, leads to compound **10** via intramolecular cyclization. Finally, the product **3aa** is achieved by the elimination primary amine of **10**.

In summary, we have developed a novel and efficient method to synthesis substituted imidazoles from vinyl azides and benzylamines under I_2/TBHP catalytic reaction system. Various substituents of vinyl azides and benzylamines tolerated well in this approach and generated the desired products in moderate to good yields.

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