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Iodine-Mediated Regioselective C–N and C–I Bonds Formation of Alkenes

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Iodine-mediated intermolecular C–N and C–I bonds formation of alkenes is described. A series of alkenes could be selectively converted into the corresponding aminoiodination products, which are versatile building blocks in organic synthesis and medicinal chemistry. Wide substrates scope, broad functional groups tolerance and easy scale-up operation make this protocol very practical and attractive in synthetic chemistry.

Alkenes are simple and abundant bulk commodities in organic synthesis, and derivatization of such feedstock materials is thus of great importance. The vicinal difunctionalization of alkenes is a class of significant reactions to rapidly increase molecular complexity with various functional groups.[1] Particularly, the catalytic aminative difunctionalization is highly attractive from the synthetic point of view owing to the remarkable biological activities of the introduced nitrogen atom.[2] In the past decade, transition metal catalyzed diamination,[3] aminooxygenation,[4] aminoboration[5] and amino-halogenation[6] have been elegantly demonstrated. Organic molecules containing vicinal halogen and amine functional groups have been found not only a basic scaffold of numerous pharmaceutically important molecules and synthetically fine chemicals,[7] but also an important precursor in the synthesis of various useful biologically active molecules.[8] Despite the significances achieved in the amino-halogenation, some challenging issues still exist: (1) A major drawback is the inevitable residual metal in the final products, which greatly restricts their application in pharmaceutical chemistry. (2) Currently, catalytic amino-halogenation dominantly focused on the relatively active alkenes such as styrenes, as well as the less unactivated chain alkenes and sterically hindered internal alkenes (cyclic alkenes) are usually hard to undergo the difunctionalization. (3) The nitrogen sources have been limited to sulfonamides, amides and carbamates so far,[9] other heterocyclic nitrogen source, such as azoles are rarely used. In terms of green and sustainable chemistry, replacement of these metal catalysts, development of efficient aminative difunctionalization approach with broad substrate scope and functional group tolerance represents a significant fundamental challenge.

Inspired and pioneered by hypervalent iodine chemistry,[10] various bond-formation methods utilizing iodide-catalyzed or mediated coupling reactions have been revealed,[11] including iodide-catalyzed or mediated difunctionalization of alkenes.[12] Aminoiodination of alkenes is an important transformation that most works have focused on intramolecular fashion, while intermolecular aminoiodination of alkenes has rarely been exploited.[13] In connection to our continued interest in C–X (X = C, N, S, I) bond formation reaction,[14] we now disclose an iodine-mediated intermolecular aminoiodination reaction of alkenes by using biological azoles as nitrogen source. In addition, the extension of this method to a gram-scale experiment was also smoothly demonstrated.

At the outset of our studies, styrene (**1a**) and 1*H*-benzotriazole (**2a**) were chosen as the model substrates to optimize the reaction conditions under air. Initially, the reaction was carried out in the presence of I_2 (1 equiv) and TBHP (*tert*-butyl hydroperoxide) (2 equiv) in EtOAc (2mL) at room temperature and afforded a 68% isolated yield of **3a** (Table 1, entry 1). Other iodine source, such as KI and nBu$_4$NI were tested, but all of them completely did not work (Table 1, entries 2–3). At this stage, we supposed that I^+ might be an active intermediate and the real iodine source. Therefore, IBr was introduced to this syetem without the addition of TBHP, and to our delight, aminoiodination product **3a** was isolated in 61% yield (Table 1, entry 4). A slight yield improvement was obtained using I_2 instead of IBr (Table 1, entry 5). Moreover, a variety of solvents were subsequently tested (Table 1, entries 6–12). DCE was proved to be the best solvent and gave the desired product **3a** in 89% (Table 1, entry 10). THF and CH_3CN were also good choise for this reaction and afforded **3a** in 78% and 71% yields, repectively. Other solvents such as H_2O and DMSO were all ineffective and no **3a** was detected (Table 1, entries 6 and 7). While an acceptable yield (56%)

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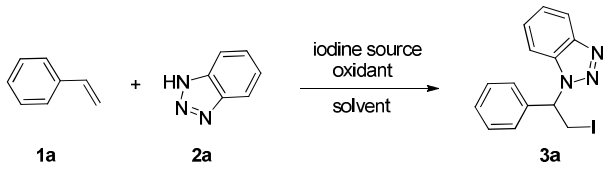
Table 1: Screening of Reaction Conditions. [a]



1a 2a 3a

Entry	Iodine source (1 equiv)	Oxidant (2 equiv)	Solvent (2 mL)	yield [b] (%)
1	I_2	TBHP	EtOAc	68
2	KI	TBHP	EtOAc	0
3	*n*BuNI	TBHP	EtOAc	0
4	IBr	no	EtOAc	61
5	I_2	no	EtOAc	66
6	I_2	no	H_2O	0
7	I_2	no	DMSO	0
8	I_2	no	THF	78
9	I_2	no	CH_3CN	71
10	I_2	no	DCE	89
11	I_2	no	EtOH	56
12	I_2	no	DCE	43[c]

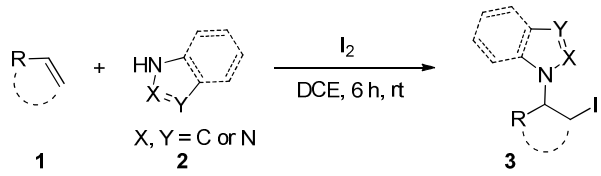
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), iodine source (0.5 mmol) and solvent (2.0 mL) at 20 °C for 6 h. [b] Yield of isolated product. [c] Reaction was performed at 40 °C.

of **3a** was obtained using EtOH as the solvent. After optimization of the reaction conditions, we established a highly efficient route for the aminoiodination of styrene (Table1, entry 10).

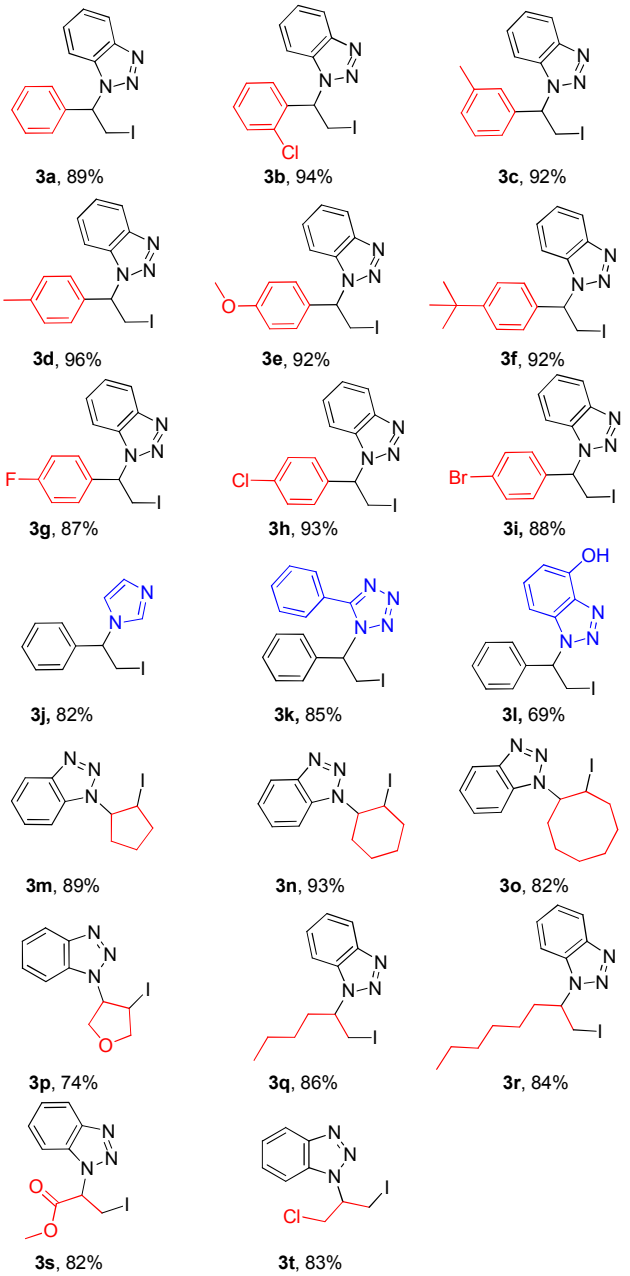
With the optimum conditions in hand, we next explored the scope of terminal styrenes under air at room temperature. The results were summarized in Scheme 1. As expected, various substitutents on the benzene ring of styrene were well tolerated, electron-donating groups (Me, MeO and *t*-Buyl) and electron-withdrawing groups (F, Cl and Br) were all furnished the transformation and gave the aminoiodination products in high efficiencies (Scheme 1). Some of these functional groups are useful for further synthetic diversification. Styrene with substitutes on different position, such as 1-chloro-2-vinylbenzene **1b**, 1-methyl-3-vinylbenzene **1c** and 1-methyl-4- vinylbenzene **1d**, could also produced the desired products in high yields (92-96%). It is noteworthy that during this aminative difunctionalization, besides **2a**, other biological azoles, imidazole **2b**, 5-phenyltetrazole **2c** and 1*H*-benzo[*d*][1,2,3]tri-azol-4-ol **2d** can offered the corresponding products **3j**, **3k** and **3l** in 82%, 85% and 69% yields, respectively.

Furthermore, the unactivated alkenes which were of chemical inertness in previously reported olefin difunctionalizations, performed well under the standard conditions (Scheme 1). *Cis*-cyclopentene **1m**, cyclohexene **1n**, and cyclooctene **1o** delivered the products **3m**, **3n** and **3o** from 82% to 93% yields**.** 2,5-Dihydro furan **1p** was also compatible with this system and offered the

Table 2: Scope of Alkenes. [a, b]

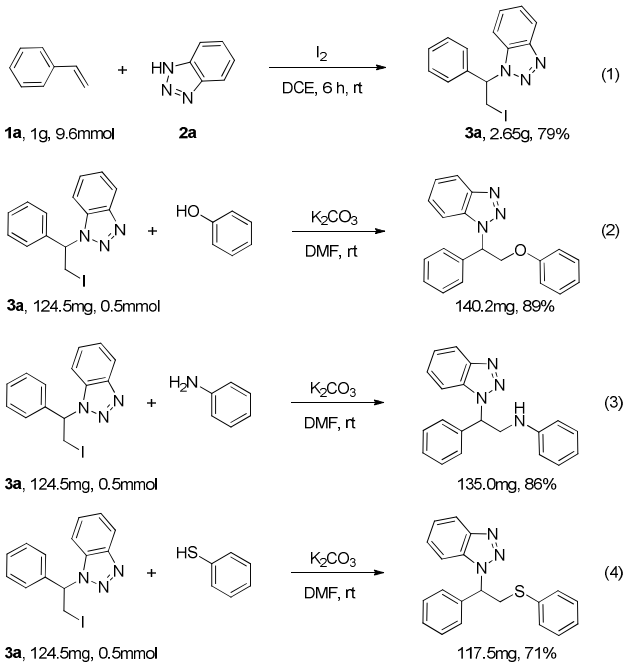


1 2 3

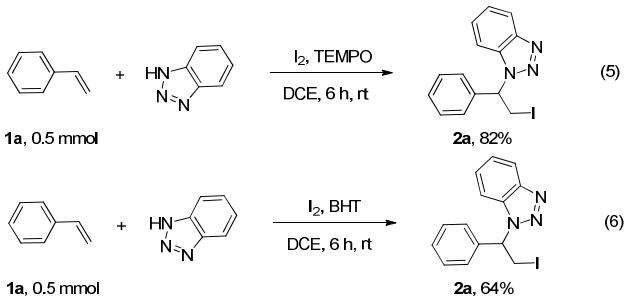


[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), I_2 (0.5 mmol), and DCE (2 mL) at 20 °C for 6 h. [b] Yield of isolated product.

desired product **3p** in 74% yield. Additionally, chain hex-1-ene **1q** and oct-1-ene **1r** were all good substrates and furnished the transformation producing the desired aminoiodination products in high efficiencies (86% and 84%). When methyl acrylate **1s** and 3-chloroprop-1-ene **1t** were tested as substrates, products **3s** and **3t** were obtained in 82% and 83% yields, respectively.



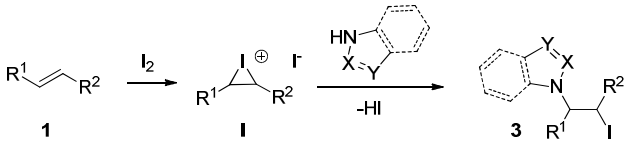
In order to prove the practicality of this approach, a gram-scale aminoiodination experiment using styrene **1a** as the substrate was performed under the optimized conditions. After 6 hours later, the desired product **3a** can be isolated in 79% yield, which suggests that it can be potentially applied in chemical industry (equiv 1). In addition, further conversion from the C–I bond to C–O, C–N and C–S bond was also easily carried out (equiv 2, equiv 3 and equiv 4).



A radical inhibition test was next carried out in order to get insight into whether the reaction proceeds via radical intermediates. When 2,2,6,6-tetramethylpiperidinooxy (TEMPO) or 2,6-*di*-*tert*-butyl-4-methylphenol (BHT), which are both known to be effective radical scavengers, was added to the reaction mixture, the desired **3a** could be obtained in 82% and 64% yields, respectively, suggesting that radical intermediates may not involved in our present aminoiodination reaction (equiv 5 and equiv 6). Besides, in sharp contrastI to KI and *n*BuNI, IBr was an active iodine source and mediated this reaction efficiently. Therefore, we supposed that I^+ was an active intermediate during this aminoiodination procedure.

According to the aforementioned information and based on previous reports, a proposed mechanism for this I_2-mediated difunctionalization of alkenes is outlined in Scheme 1. Initially, the substrate alkene reacts with I_2 to afford the iodonium ion intermediate **I**, which undergoes regioselective ring opening with azoles giving the the desired iodo products **3**. The iodide ion is then reoxidized with TBHP to regenerate I_2 for the next catalytic cycle.

Scheme 1: Proposed reaction mechanism.



Conclusions

In summary, we have developed an efficient iodine mediated intermolecular aminoiodination of alkenes under mild reaction conditions. This protocol provides a valuable synthetic tool for simultaneously introduction biological azoles and iodine to a wide range of alkenes, which are expected to be useful intermediates for the preparation of pharmaceutically and biologically active compounds as well as functional materials. Easy scale-up operation make this protocol very practical and attractive in synthetic chemistry.

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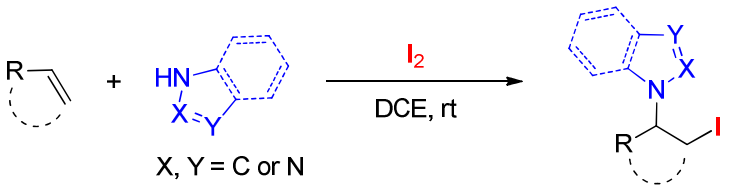

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