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# Hypervalent iodane mediated reactions of *N*-acetyl enamines for the synthesis of oxazoles and imidazoles†

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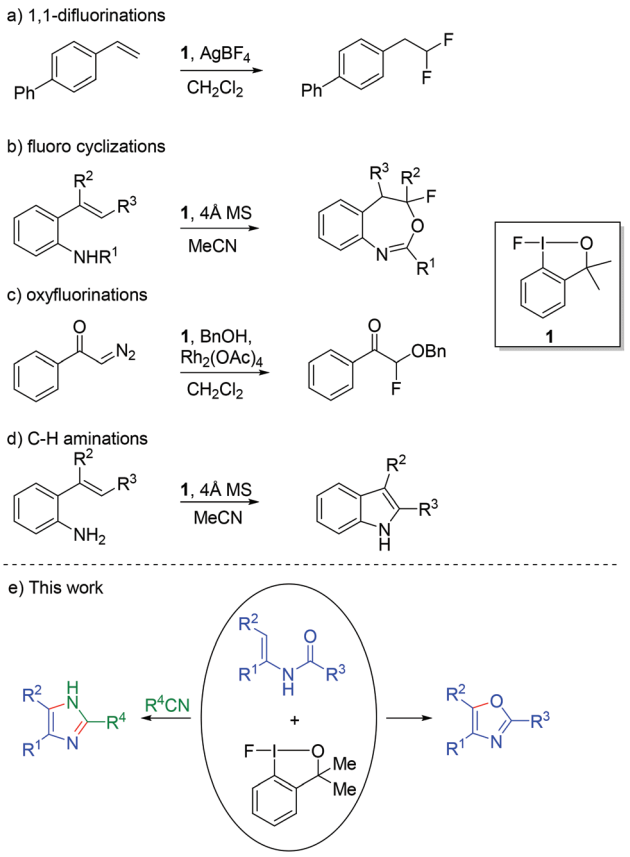
**A hypervalent iodane reagent used for the intramolecular cyclization of *N*-acetyl enamines and intermolecular cyclocondensation of enamines and nitriles was investigated. The reaction was performed under mild conditions and gave oxazoles and imidazoles, respectively, in moderate to excellent yields. This transformation exhibits good reactivity, selectivity and functional group tolerance. The selectivity of the intra- or intermolecular reaction is dependent on the structure of *N*-acetyl enamines.**

## Introduction

Oxazole and imidazole derivatives are significant structural motifs in natural products[1] and pharmaceutical compounds.[2] Consequently, the synthesis of these compounds has received extensive attention from researchers. For the synthesis of oxazoles, many strategies have been reported, such as condensation,[3] cyclization,[4] transition-metal-catalyzed addition of diazo compounds to nitriles,[5] and oxidation of oxazolines.[6] The classic method for the synthesis of imidazoles is the Debus–Radziszewski reaction.[7] In recent years, a large number of transition-metal-catalyzed approaches have been widely applied to synthesize imidazole derivatives.[8] However, the construction of oxazoles or imidazoles through a selective intra- or intermolecular reaction controlled by the substituents of substrates has seldom been reported.

Hypervalent iodane reagents have been used for alkene functionalization over the past several decades.[9] Recently, a variety of iodine-based reagents[10] and catalytic systems[11] have been accessible, allowing for the construction of highly versatile building blocks. With the synthesis of the bench stable fluorobenziodoxole **1** in 2013 by Togni[12] and Stuart,[13] the new hypervalent iodane reagent has emerged as an efficient and widely used reagent in fluorination reactions. This reagent was successfully applied in intra- and intermolecular fluorofunctionalization,[14] difluorination[15] and even radiofluorination reactions[16] (Scheme 1a). In addition to being an important alternative to electrophilic fluorinating reagents, it also shows new reactivity and selectivity in alkene functionalization reactions. Gulder and coworkers investigated the application of




**Scheme 1** Applications of fluorobenziodoxole **1**.

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fluorobenziodoxole **1** in the fluorocyclization of styryl benzamides to form 4-fluoro-1,3-benzoxazepines.[17] In 2018, Rehbein and Gulder reported that styryl benzamides could undergo C–H amination and C–H fluorination pathways in the presence of fluorobenziodoxole **1** to generate indoles and 4-fluoro-1,3-benzoxazepines. They investigated the mechanism of these transformations and disclosed that the difference in selectivity could be controlled by the *N*-substituents.[18]

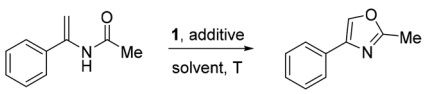
We are interested in the unique properties of fluorobenziodoxole **1** and would like to investigate the reaction of *N*-acetyl enamines[19] in the presence of **1**. In this communication, we report the application of fluorobenziodoxole **1** for the cyclization of *N*-acetyl enamines and intermolecular cyclocondensation reaction of enamines and nitriles to synthesize multi-substituted oxazoles and imidazoles (Scheme 1b).

## Results and discussion

Initially, we performed the reaction using *N*-(1-phenylvinyl) acetamide **2a** as a substrate and applied the conditions which successfully realized the conversion of styryl benzamides to fluoro-benzoxazepine and indoles.[17,18] To our disappointment, neither the fluorocyclization product nor the oxazole product was observed under these standard conditions (Table 1, entries 1 and 2). The reaction did not take place without an additive and most of the starting material was recovered (entry 3). We then found that the reactivity was improved when different Lewis acids were added to the reaction mixture (entries 4–6). The reaction yield was increased to 42% when $BF_3{\cdot}OEt_2$ was used. If the reaction was performed with 4 Å molecular sieves and 10 mol% $BF_3{\cdot}OEt_2$, the product **3a**[20] could be obtained in 81% yield (entry 7). Lower yields were achieved when using dichloromethane (DCM) or methanol as the solvent (entries 8 and 9). The reaction did not occur when toluene was used as the solvent (entry 10). The yields slightly decreased when the reaction was performed at higher temperatures (entries 11 and 12). The reaction also gave oxazole products while using other hypervalent iodane reagents, such as $PhI(OAc)_2$ or $PhI(OCOCF_3)_2$, but the yields were much lower (entries 13 and 14).

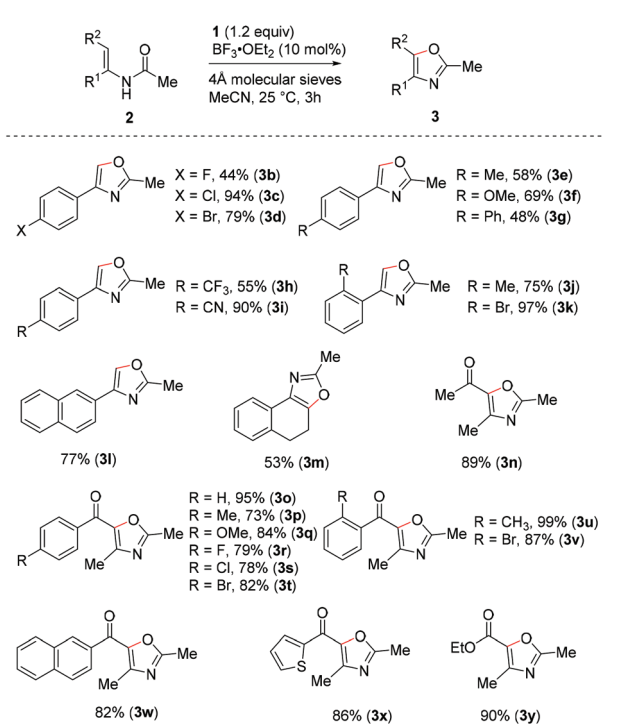
With the optimized reaction conditions in hand, we moved on to examine the reaction of *N*-acetyl enamines bearing different substituents (Scheme 2). We first investigated the substrates in which $R^1$ is an aromatic group and $R^2$ is hydrogen. The reaction proceeded well when halogen substituents such as fluoro, chloro, and bromo were at the *para*-position of the benzene ring and gave the products in 44–94% yields (**3b–3d**).[21] The substrates with electron-donating groups participated in this reaction and gave the oxazole products in moderate yields (**3e** and **3f**). Substrates with electron-withdrawing groups, such as trifluoromethyl and cyano groups, were well tolerated under the reaction conditions and the corresponding products were obtained in 55% and 90% yields, respectively. When the substituents were at the *ortho*-position, the reaction proceeded and provided the products in good to excellent yields (**3j** and **3k**). The $R^1$ group of enamine, 2-naphthyl, also exhibited good reactivity under the reaction conditions and

**Table 1** Optimization of reaction conditions[a]



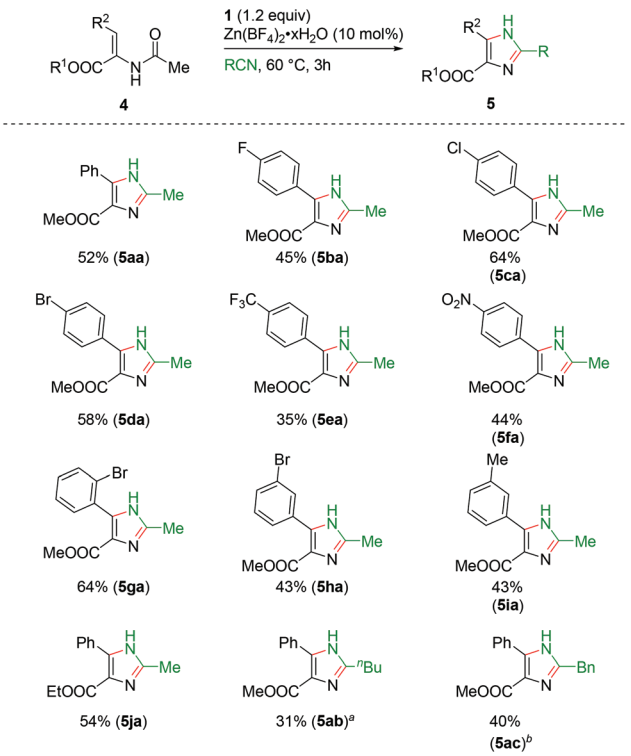

| Entry | Additive | Solvent | $T$ (°C) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 4 Å MS | MeCN | 25 | <5 |
| 2 | CSA | MeCN | 25 | <5 |
| 3 | — | MeCN | 25 | n.d. |
| 4 | $Zn(BF_4)_2$ | MeCN | 25 | 29 |
| 5 | $BF_3{\cdot}OEt_2$ | MeCN | 25 | 42 |
| 6 | $AgBF_4$ | MeCN | 25 | 24 |
| 7 | 4 Å MS $BF_3{\cdot}OEt_2$ | MeCN | 25 | 81 (64)[c] |
| 8 | 4 Å MS $BF_3{\cdot}OEt_2$ | DCM | 25 | 53 |
| 9 | 4 Å MS $BF_3{\cdot}OEt_2$ | $CH_3OH$ | 25 | 22 |
| 10 | 4 Å MS $BF_3{\cdot}OEt_2$ | Toluene | 25 | n.d. |
| 11 | 4 Å MS $BF_3{\cdot}OEt_2$ | MeCN | 40 | 60 |
| 12 | 4 Å MS $BF_3{\cdot}OEt_2$ | MeCN | 60 | 59 |
| 13 | 4 Å MS $BF_3{\cdot}OEt_2$ | MeCN | 25 | 22[d] |
| 14 | 4 Å MS $BF_3{\cdot}OEt_2$ | MeCN | 25 | 26[e] |

[a] The reactions were carried out using **2a** (0.2 mmol, 1 equiv.) and fluoroiodane **1** (1.2 equiv.) and an additive (10 mol% Lewis acid) in the solvent (0.1 M). [b] The yields were determined by $^1H$ NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yields. [d] $PhI(OAc)_2$ was used instead of **1**. [e] $PhI(OCOCF_3)_2$ was used instead of **1**. MS = molecular sieves; CSA = camphorsulfonic acid; n.d. = not determined.



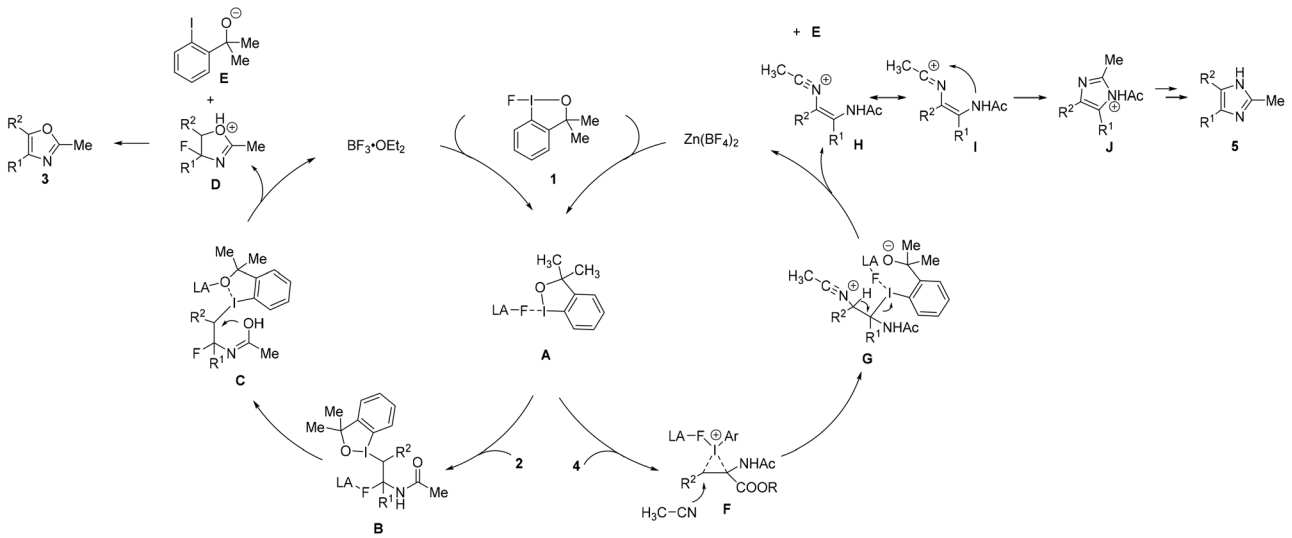

**Scheme 2** Intramolecular cyclization of *N*-acetyl enamines. The reaction was carried out using *N*-acetyl enamine **1** (0.2 mmol, 1 equiv.), fluoroiodane reagent (0.24 mmol, 1.2 equiv.), and $BF_3{\cdot}OEt_2$ (0.02 mmol, 10 mol%) in MeCN (0.1 M). Products **3n–3y** were obtained at 60 °C.

the product was obtained in 77% yield (**3l**). *N*-(3,4-Dihydronaphthalen-1-yl)acetamide underwent the cyclization reaction and afforded the tricyclic ring product (**3m**). We then explored the reaction of various enamine derivatives in which $R^1$ is a methyl group and $R^2$ is an acyl group. When the acetyl group was introduced to the substrate, the reaction gave the product in 89% yield (**3n**). The enamine with a benzoyl group participated in this reaction smoothly and the oxazole product was obtained in 95% yield (**3o**). Substrates with different substituents, including methyl and methoxyl groups and halogen, at the 4-position of the benzene ring were tolerated well and provided the desired products in good yields (**3p–3t**). Good to excellent yields were achieved when the substituents were at the 2-position of the benzene ring (**3u–3v**). The substrates with 2-naphthoyl or 2-thienyl groups underwent cyclization efficiently and the products were afforded in 82% and 86% yields (**3w–3x**), respectively. The reaction also proceeded when $R^2$ was an ester group and the oxazole product could be obtained in 90% yield (**3y**).




**Scheme 3** Intermolecular cyclocondensation of *N*-acetyl enamines and nitriles. The reaction was carried out using *N*-acetyl enamine **1** (0.2 mmol, 1 equiv.), fluoroiodane reagent (0.24 mmol, 1.2 equiv.), and $Zn(BF_4)_2{\cdot}xH_2O$(0.02 mmol, 10 mol%) in MeCN (0.1 M). [a] *n*-Pentanenitrile was used as the solvent. [b] Phenylacetonitrile was used as the solvent.

Then, we further extended the substrate to the *N*-acetyl enamine **4a** in which a methyl ester group was introduced. Under the standard reaction conditions, no product was observed. The substrate **4a** is much less electron-rich than **2**, and it may require higher temperature. We screened the reaction conditions[22] and found that in the presence of $Zn(BF_4)_2{\cdot}xH_2O$ at 60 °C, the cyclocondensation reaction of **4a** and $CH_3CN$ occurred and the imidazole product **5aa** was obtained in 52% yield. The halogen substituents could be tolerated under these reaction conditions and afforded the corresponding products in moderate yields (**5ba–5da**).[23] Substrates bearing electron-withdrawing groups such as trifluoromethyl and nitryl groups at the *para* position of the benzene ring gave the products in lower yields (**5ea–5fa**). Substrates with the substituents at the *ortho* and *meta* positions of the benzene ring also underwent the cyclization reaction and provided the products in 43–64% yields (**5ga–5ia**). When $R^1$ of the substrate was an ethyl ester group, the reaction proceeded and gave a similar result to the model reaction (**5ja**). The reaction was also performed using *n*-pentanenitrile and phenylacetonitrile as solvents; the reaction occurred and the corresponding imidazole products were obtained but with lower yields (**5ab** and **5ac**) (Scheme 3).




**Scheme 4** Proposed reaction mechanism.

According to a reported study[24] and our experiments, we proposed the reaction mechanism for the intramolecular cyclization and intermolecular cyclocondensation reactions (Scheme 4). First, the fluoroiodane **1** is activated by a Lewis acid to form intermediate **A**, in which the fluorine is coordinated to the Lewis acid. Then, substrate *N*-acetyl enamine **2** enters and engages in a metathesis reaction with **A** and leads to the formation of intermediate **B**. An intramolecular nucleophilic attack occurs to form a five-membered ring intermediate **D** and release the iodine **E**. Finally, deprotonation and elimination of HF give the product **3**. If the substrate is enamine **4**, in which the C–C double bond is much less electron-rich than that in substrate **2**, the formation of an iodonium ion **F** instead of a metathesis reaction is observed. The intermediate **F** undergoes an intermolecular nucleophilic attack by $CH_3CN$ to generate intermediate **G**, the elimination of **E** and the Lewis acid to form **H** and then after intramolecular cyclization and elimination of the acetyl group to give imidazole product **5**.

## Conclusions

In summary, we have developed intramolecular cyclization of *N*-acetyl enamines and intermolecular cyclocondensation reaction of enamines and nitriles by using hypervalent fluoroiodane reagent **1**. The reaction was performed under mild conditions and afforded the oxazole and imidazole products in moderate to excellent yields. A variety of functional groups could be tolerated well under the reaction conditions. The reaction mechanism was proposed and the selectivity of the intra- or intermolecular reaction could be controlled by the molecular properties of substrates.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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