Synthesis of 4-Imidazolidinones from Diamides and Ethynyl Benziodoxolones vis Double Michael Addition: Ethynyl Benziodoxolones as Electrophilic Ynol Synthons

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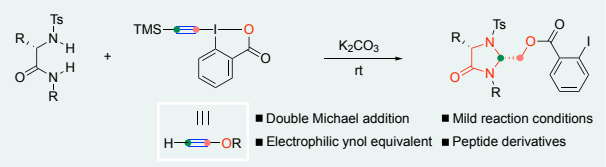
Supporting Information Placeholder



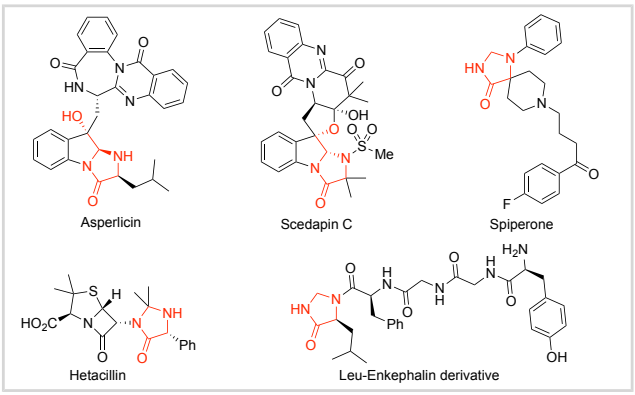
ABSTRACT: The moiety of 4-imidazolidinone is an important structural motif in organic synthesis and medicinal chemistry. We present the synthesis of 4-imidazolidinones from various diamides with ethynyl benziodoxolones through double Michael addition, which is an unprecedented reaction mode for hypervalent alkynyl iodine compounds. *cis*-2,5-disubstituted 4-imidazolidinones were diastereoselectively synthesized from amino-acid-derived diamides. Having derivatized the 4-imidazolidinones, several control experiments and density functional theory calculations were conducted to realize mechanistic insight.

The 4-imidazolidinone structure is an important motif that exists in many bioactive natural products, such as asperlicin and scedapin C[1] (Figure 1), particularly where such compounds bear an alcohol moiety at the 2-position of the 4-imidazolidinone. Medicinal and biologically active compounds, such as spiperone and hetacillin, also have the 4-imidazolidinone structure[2] (Figure 1). Furthermore, the introduction of 4-imidazolidinone structures changes the activity and stability of peptides, such as Leu-enkephalin (Figure 1), vancomycin, and cyclic peptides.[3] Additionally, 4-imidazolidinones have been used as chiral organocatalysts,[4] ligands,[5] and synthetic intermediates.[6] Accordingly, there are numerous synthetic methods available to access 4-imidazolidinones.[7–8] The most general and straightforward method is via the condensation of α-amino amides with aldehydes and ketones.[9] However, this reaction generally requires harsh reaction conditions, such as strong acids, high temperature, and/or excess amounts of aldehyde and ketone plus the removal of water and multiple steps. In 2016, Bode et al.[9a] reported the construction of 4-imidazolidinone as a mixture of diastereomers under mild conditions via an aldehyde conjugation reaction using amino hydrazide and amino hydroxamic acid. Furthermore, Raj et al.[3a] reported the "CyClick" strategy, which involves the intramolecular construction of 4-imidazolidinones in a cyclic peptide, which enables their construction under mild conditions. Thus, the synthesis of 4-imidazolidinones under mild reaction conditions has potential for use as a chemical biology tool and in terms of its intrinsic synthetic value.

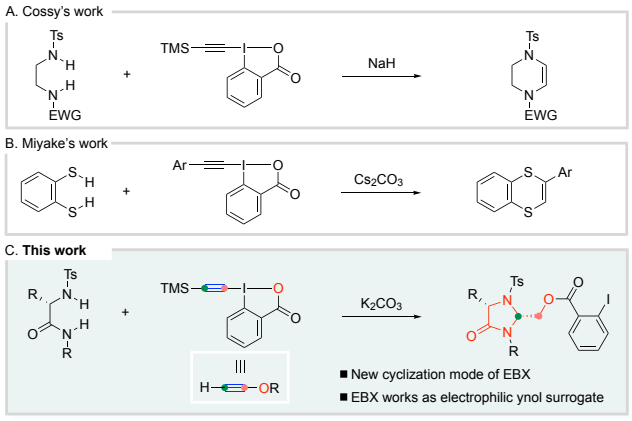
Hypervalent alkynyl iodine compounds have been used for the synthesis of various heterocycles by Michael addition and cyclization via alkylidene carbene or alkyne under mild reaction conditions due to the high electron-withdrawing nature and hyper-leaving-group character of the λ[3]-iodanyl group.[10–13] Furthermore, the chemistry of benziodoxol(on)e reagents has recently attracted considerable interest because of their higher stability compared with their acyclic analogs.[14] Alkynyl benziodoxolones have also been used for the synthesis of heterocycles (with and without metal catalysts).[15–16] In 2013, Cossy et al.[16a] reported the synthesis of tetrahydropyrazines from diamides using trimethylsilyl ethynyl benziodoxolone (TMS-EBX) in the presence of a strong base through 6-*endo*-*dig* cyclization of the ynamide intermediate[16a] (Scheme 1A). Furthermore, during the course of our investigations, Miyake et al.[16b] reported the synthesis of 1,2-dithio-1-alkenes, including benzene-1,2-dithiol as a substrate to benzo-1,4-dithiines, using EBX reagents by intramolecular thiyl radical addition to thiol-substituted vinyl benziodoxolones[17–18] (Scheme 1B). Recently, due to our interest in the development of the reaction with hypervalent iodine compounds,[19] we reported the synthesis of *cis*-β-amide-vinylbenziodoxolones from sulfonamide, including amino-acid derivatives, with an ethynyl benziodoxolone–chloroform complex.[19a] Based on the results of the aforementioned studies, we hypothesized that the reaction of an amino-acid-derived diamide with ethynyl benziodoxolone would afford 4-imidazolidinone by sequential intermolecular and intramolecular double Michael addition, which is, to the best of our knowledge, an unprecedented reaction mode of hypervalent alkynyl iodine compounds (Scheme 1C). After the cyclization, the benziodoxolone may convert to 2-iodobenzoate, which is an atom-economical reaction because

2-iodobenzoate moiety serves as a versatile handle for further transformations[20] (Scheme 1C). Double Michael additions have been used for the construction of various cyclic compounds[21]; however, to our knowledge, the synthesis of 4-imidazolidinone by such means has not been reported. Herein, we report straightforward access to 4-imidazolidinones from diamides using TMS-EBX or EBX-MeCN through a double Michael addition reaction and a formal reductive elimination sequence (Scheme 1C). Interestingly, the EBX reagents worked as an electrophilic ynol surrogate, which had umpolung reactivity to a normal nucleophilic ynol[22] (Scheme 1C).

Figure 1. 4-Imidazolidinone in bioactive natural products, medicine, and a prodrug.



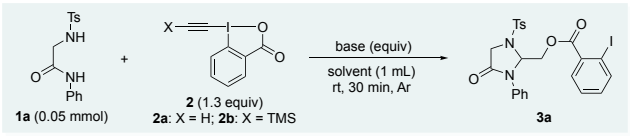
Scheme 1. Previous and this work



To explore our hypothesis, we initially attempted the reaction with glycine-derived diamide **1a** as the substrate (Table 1). When EBX-MeCN complex (**2a**), prepared from TMS-EBX (**2b**),[19e] was used, all solvents gave 4-imidazolidinone (**3a**) in moderate to good yields (entries 1–5). However, **2b** gave more solvent-dependent results (entries 6–10). Among the solvents we used, mixed solvent (IPA/MeCN = 1:1) gave the best isolated yield (80%) with **2b** (entry 7). A screening of bases with **2b** revealed that sodium carbonate and cesium carbonate also gave the desired product in good yields (entries 11 and 12). However, organic bases gave lower product yields (entries 13 and 14), and in the absence of a base, no reaction occurred (entry 15). Additionally, an increase in the amount of base did not improve the yield for the synthesis of **3a** (entries 16 and 17). Consequently, the optimal reaction conditions were identified as follows: treatment of **1a** with **2b** (1.3 equiv.) in the presence of K_2CO_3 (0.1 equiv.) in IPA/MeCN (1:1 *v/v*) at room temperature for 30 min (entry 7). Note that **3a** was also synthesized at the 1 mmol scale with 84% yield, indicating the scalability of the reaction (entry 7).

With the optimized reaction conditions in hand, we examined the scope and limitations of the reaction system (Scheme 2). Under the optimized conditions, 2-nitrobenzenesulfonamide was transformed into the corresponding product **3b** in low yield (24%); however, extending the reaction time to 24 h gave an improved yield (59%). Conversely, carbamate **1c** was recovered unchanged probably because of its low acidity.[16a,19a] Furthermore, the reactions of bromo-, iodo-, and methyl-substituted aniline derivatives afforded the corresponding products in good yields regardless of the position of the substituent (**3d**–**3h**).

Table 1. Study of reaction conditions[a]



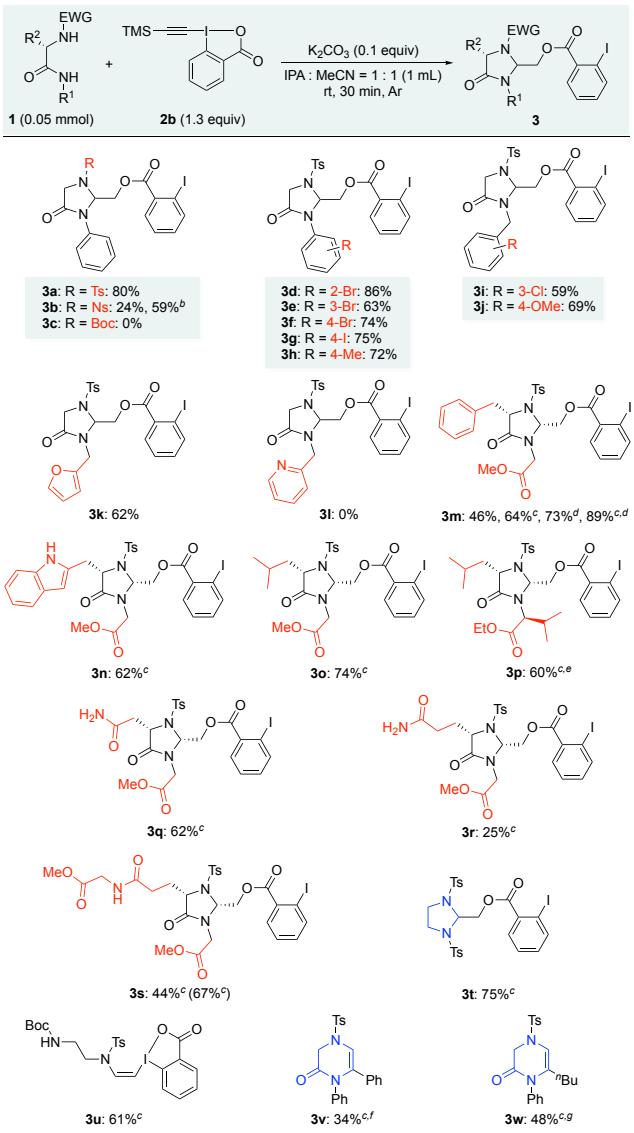
entry	2	base (equiv)	solvent	yield (%)
1	**2a**	K_2CO_3 (0.1)	IPA	68
2	**2a**	K_2CO_3 (0.1)	IPA:MeCN=1:1	(77)
3	**2a**	K_2CO_3 (0.1)	MeCN	68
4	**2a**	K_2CO_3 (0.1)	AcOEt	49
5	**2a**	K_2CO_3 (0.1)	CH_2Cl_2	46
6	**2b**	K_2CO_3 (0.1)	IPA	0
7	**2b**	K_2CO_3 (0.1)	IPA:MeCN=1:1	(80), (84)[b]
8	**2b**	K_2CO_3 (0.1)	MeCN	66
9	**2b**	K_2CO_3 (0.1)	AcOEt	12
10	**2b**	K_2CO_3 (0.1)	CH_2Cl_2	5
11	**2b**	Cs_2CO_3 (0.1)	IPA:MeCN=1:1	78
12	**2b**	Na_2CO_3 (0.1)	IPA:MeCN=1:1	77
13	**2b**	Et_3N (0.1)	IPA:MeCN=1:1	44
14	**2b**	pyridine (0.1)	IPA:MeCN=1:1	0
15	**2b**	-	IPA:MeCN=1:1	0
16	**2b**	K_2CO_3 (0.2)	IPA:MeCN=1:1	79
17	**2b**	K_2CO_3 (1.0)	IPA:MeCN=1:1	79

[a]Reaction conditions: **1a** (0.05 mmol), **2** (0.065 mmol), base, solvent (1 mL), room temperature, 30 min, argon. Yields were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. Numbers in parentheses are isolated yields. [b]1 mmol scale.

Moreover, the reaction proceeded with benzylamine derivatives bearing electron-withdrawing and electron-donating groups (**3i**, **3j**). While a furan substituent was also well tolerated (**3k**), a pyridine substituent resulted in a complex mixture but no corresponding final product was obtained (**3l**). Pleasingly, dipeptide **1m** gave the corresponding *cis*-2,5-disubstituted 4-imidazolidine (**3m**) diastereoselectively in moderate yield (46%) under the optimized conditions. Interestingly, an improved yield of **3m** (64%) was obtained using 1 equiv. of K_2CO_3. Furthermore, using EBX-MeCN instead of TMS-EBX gave a better yield of **3m** (46% vs. 73% and 64% vs. 89%). This result indicated that unprotected EBX-MeCN shows better reactivity to some substrates, which allows addition reactions without deprotection of TMS under mild conditions. Note that no *trans*-2,5-disubstituted 4-imidazolidines were detected via crude ^{1}H NMR. Other dipeptides also gave the corresponding products in moderate to good yields with 1 equiv. K_2CO_3 (**3n**–**3r**).

Furthermore, other functionalities, such as indole, amide, and ester groups, were well tolerated. **1r** gave the many undetermined by-products and a low isolated yield (25%) of **3r**. However, the isolated yield of **3s** was diminished in the separation step with preparative TLC, probably because of the high polarity of **3s**. Importantly, **3n** was determined to have an *ee* of >99% by HPLC using CHIRALPAK IG. Furthermore, tripeptide **1s** also gave **3s** in moderate yield using 1 equiv. of K_2CO_3. Interestingly, six- and seven-membered rings were not detected by ^{1}H NMR when asparagine, glutamine, and glutamic acid derivatives were used (**3q**–**3s**). Furthermore, bis-tosyl-ethylenediamine gave the corresponding product (**3t**), indicating that this reaction mode is not limited to the synthesis of 4-imidazolidinones. Conversely, the Ts-Boc-ethylenediamine gave the labile *cis*-β-substituted vinylbenziodozolone (**3u**) in 61% yield along with an undetermined impurity. This result could indicate that tosylamide initially adds to the β-position of EBX to produce the vinyl

Scheme 2. Scope and limitations of the synthesis of 4-imidazolidinone[a]

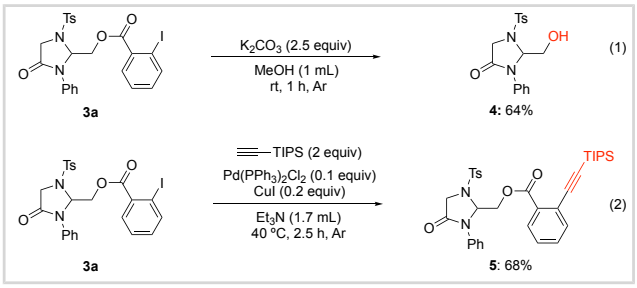


[a]Reaction conditions: **1** (0.05 mmol), **2b** (0.065 mmol), K_2CO_3 (0.005 mmol), 1-propanol (0.5 mL), acetonitrile (0.5 mL), room temperature, 30 min, argon. Isolated yields. Numbers in parentheses are ^{1}H NMR yields using 1,1,2,2-tetrachloroethane as an internal standard. [b]Reaction time is 24 h. [c]K_2CO_3 (0.05 mmol). [d]**2a** was used instead of **2b**. [e]**1p** (11%) was recovered. [f]Ph-EBX (**2c**) was used instead of **2b**. [g]^{n}Bu-EBX (**2d**) was used instead of **2b**.

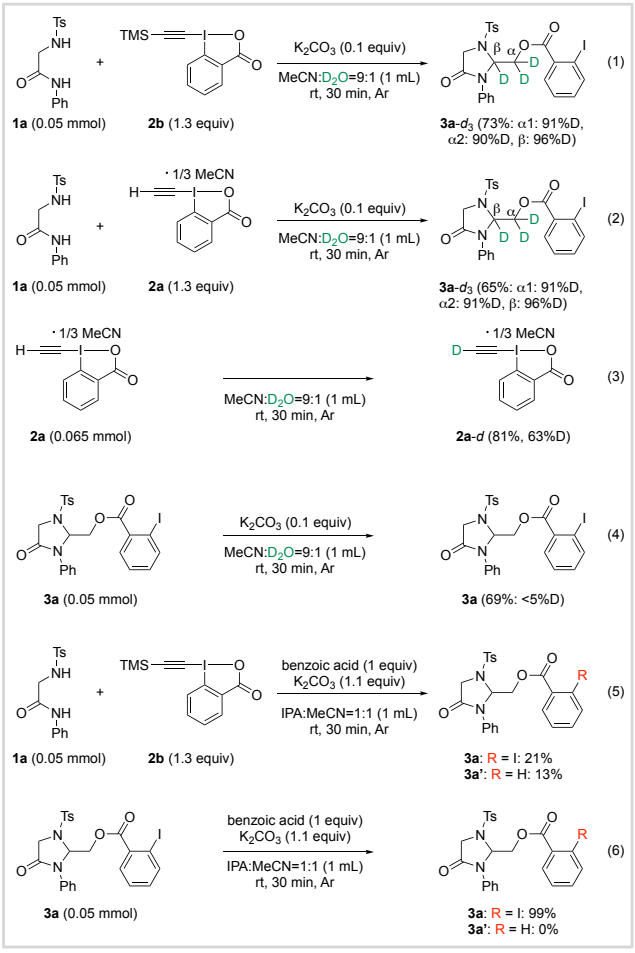
benziodoxolone, and intramolecular cyclization gave the 4-imidazolidinone. Interestingly, phenyl- and butyl-substituted EBX (**2c**, **2d**) gave no 4-imidazolidines, and 3,4-dihydropyrazin-2-one[23] was obtained by regioselectively, albeit in moderate yield, probably via an ynamide intermediate (**3v**, **3w**).[16a] These results indicated that the use of an unsubstituted EBX reagent is essential for the successful synthesis of 4-imidazolidinones in this system. Note that these 4-imidazolidinones are all novel compounds.

It is noteworthy that glycine-derived 4-imidazolidinone **3a** was further derivatized (Scheme 3). Alcohol **4** was obtained by solvolysis in the presence of K_2CO_3 in MeOH.[24] Furthermore, the Sonogashira reaction was conducted at the 2-iodobenzoic

Scheme 3. Derivatization of 4-imidazolidinone



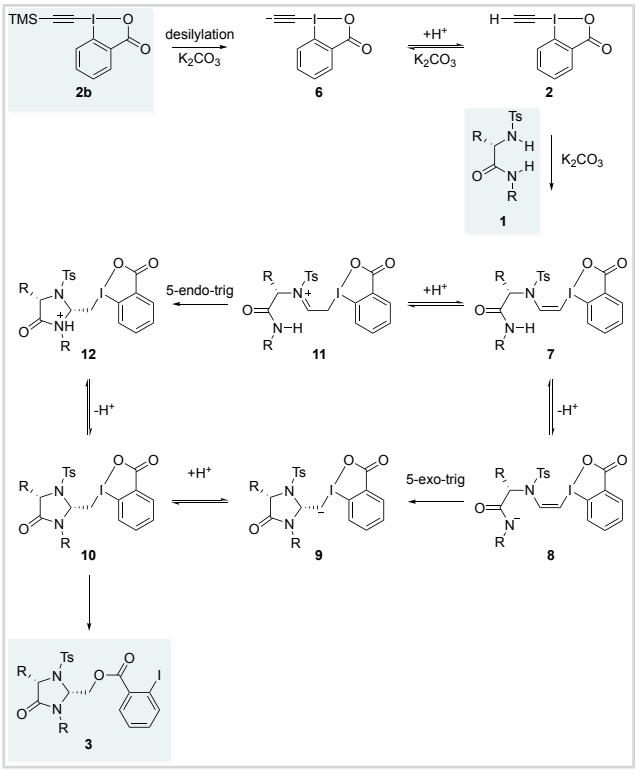
Scheme 4. Control experiment



acid moiety to give alkyne **5**.[20b]

Several experiments were conducted with **1a** to elucidate the reaction mechanism. Upon reaction using MeCN/D_2O = 9:1 as a solvent, **2b** afforded 4-imidazolidinone (**3a**-d_3) in good yield with high deuterium incorporation (equation 1, Scheme 4). Note that deuterium was not incorporated at the α-position of the carbonyl group of the amide (equation 1, Scheme 4). Furthermore, **2a** gave a similar result (equation 2, Scheme 4). Interestingly, **2a** gave **2a**-*d* in 81% yield with 63% deuterium incorporation, even in the absence of a base, due to the highly electron-withdrawing nature of the λ^3-iodanyl group (equation 3, Scheme 4). Conversely, when **3a** was used as the substrate under the same conditions, no deuterium was incorporated (equation 4, Scheme 4). These results indicated that **2b** converts to EBX upon deprotection of the TMS group via the relatively

Scheme 5. Plausible reaction mechanism



stable acetylide anion of EBX. Furthermore, the acetylenic hydrogen of **2a** was rapidly abstracted in the presence of catalytic amounts of K_2CO_3 prior to the conjugate addition of **1a** to give the trideuterated product **3a**-d_3. Furthermore, when we performed the reaction in the presence of benzoic acid, a mixture of the expected products **3a** and **3a'** was obtained (equation 5, Scheme 4). In contrast, **3a** gave no **3a'** under the same conditions (equation 6, Scheme 4), indicating that intermolecular substitution of an alkyl benziodoxolone intermediate by benzoic acid in the presence of the base was a likely reaction pathway to give the 4-imidazolidinone **3a'**.

Based on these results and those from previous studies, a plausible mechanism for the synthesis of 4-imidazolidinone was formulated (Scheme 5). TMS-EBX (**2b**) is deprotected to EBX in the presence of K_2CO_3 due to the high stability of the acetylide anion (**6**). The sulfonamide moiety of diamide **1** adds to the β-carbon of **2** in the presence of K_2CO_3 because of the higher acidity of the sulfonamide than that of the amide to form *cis*-VBX **7**, probably through the coordination of the sulfonamide to the iodine center.[18a] Regrettably, we could not isolate the corresponding VBX from **1a**–**1t**; however, the formation of **3u** evidenced the formation of VBX as an intermediate. For the cyclized intermediate **10**, 5-*endo-trig* and/or 5-*exo-trig*, cyclization is probably possible. To gain further insight into the reaction mechanism of the cyclization step, density functional theory (DFT) calculations were performed using Gaussian16, Revision C.01.[25] The possible mechanistic routes were analyzed in terms of solvation-corrected Gibbs free energies. The results demonstrated that 5-*exo-trig* cyclization from **8** to **9**, which is a favored mode by Baldwin's rules,[26] has a lower free energy barrier ($\Delta G^{\ddagger}$ = 13.8 kcal mol^{-1}) than that of 5-*endo-trig* cyclization from **11** to **12** ($\Delta G^{\ddagger}$ = 20.8 kcal mol^{-1})(Figure S6). In addition, the energy difference between the deprotonation of amide **7** to anion **8** was 61.2 kcal mol^{-1} lower than the protonation of **7** to cation **11,** possibly due to the highly electron deficient nature of **11**. Although other cyclization mechanisms, such as via a

betaine intermediate, cannot be excluded, the formation of betaine from **7** requires 33.3 kcal mol^{-1} (see the SI for details). These results indicate that 5-*exo*-*trig* cyclization; that is, intramolecular Michael addition, was the most likely pathway. Finally, alkyl benziodoxolone **10** was probably converted to **3** through rapid intermolecular substitution by 2-iodobenzoic acid, probably initially generated by the decomposition of benziodoxolones, in the presence of a base due to the hyper-leaving-group ability of the λ^3-iodanyl group, as indicated by the control experiment.[27] However, intramolecular reductive elimination cannot be ruled out.

In conclusion, we achieved the efficient synthesis of 4-imidazolidinones from a variety of diamides by double Michael addition, a novel reaction mode for hypervalent alkynyl iodine compounds, and a formal reductive elimination sequence using *in situ*-generated EBX from TMS-EBX or EBX-MeCN. The highly reactive EBX enabled chemoselective intermolecular *N*-alkenylation of the sulfonamide moiety and intramolecular cyclization of the amide moiety under mild basic conditions. The reaction diastereoselectively gave *cis*-2,5-disubstituted 4-imidazolidinones from amino-acid-derived diamides. Furthermore, 2-[(2-iodobenzoyloxy)methyl]-4-imidazolidinone was derivatized by solvolysis and Sonogashira coupling. DFT calculations indicated that the double Michael addition mechanism is plausible. Thus, the potential of an unsubstituted EBX reagent for the synthesis of heterocycles from complex molecules and their functionalization with mild nucleophiles was demonstrated.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data (PDF).

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Notes

The authors declare no competing financial interest.

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