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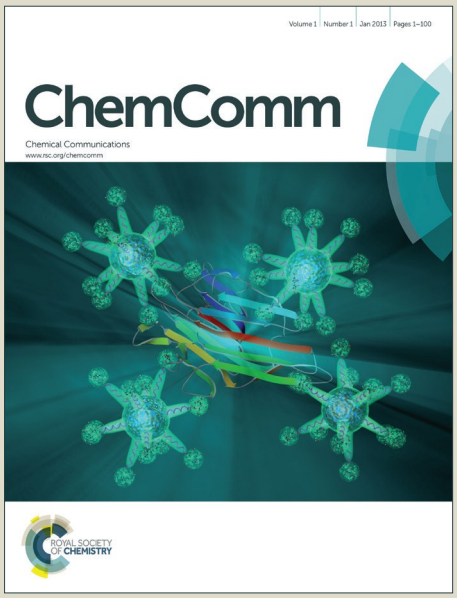

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Regioselective Iodoamination of Terminal Ynamides for the Synthesis of *α*-amino-*β*,*β*-diiodo-enamides

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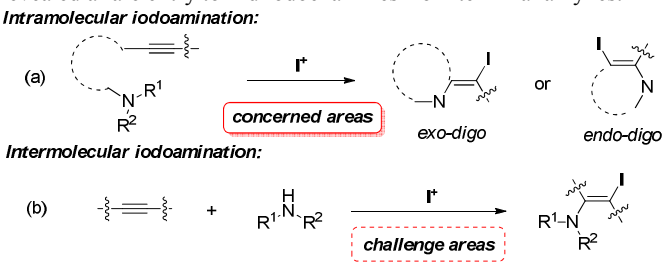
A mild and efficient methodology concerning I_2/TBHP-mediated intermolecular iodoamination of ynamides with amines for the synthesis of *α*-amino-*β*,*β*-diiodo-enamides was developed. This reaction provides the first intermolecular iodoamination of terminal alkynes to diiodo-enamines and can be easily applied to a wide range of substrates.

1,1-Dihalo-1-alkenes are not only important structural motifs frequently occurring in natural compounds and pharmaceuticals,[1] but also useful and versatile building blocks for organic synthesis, widening the road to the synthesis of heterocyclic compounds like the synthesis of 2-oxazolones,[2] indoles,[3] benzofurans,[4] benzothiophenes[5] and others.[6] The most popular synthesis of 1,1-dihalo-1-alkenes concerns the Wittig type reaction between carbonyl compounds and tetrahalocarbon.[7] However, this protocol was always limited to the synthesis of some special structures. Thus, the development of other practical synthetic methods for 1,1-dihalo-1-alkenes is highly desirable. And up to now, numerous efforts have been devoted to the achievement of such a goal. For examples, head-to-tail coupling of 1-iodoalkynes,[8] iodine mediated electrophilic addition of 1-iodoalkynes[9] and others.[10]

Enamines on one hand are versatile tools providing key intermediates for the synthesis of nitrogen-containing compounds in organic synthesis.[11] And the most popular synthesis of 1,2-disubstituted enamines was focused on the condensation of amines with ketones or aldehydes[12] and metal catalyzed hydroamination of alkynes.[13] On the other hand, as shown in **Scheme 1**, intramolecular iodoamination (iodine mediated addition of amines to alkynes) of alkynes is one of the most powerful methodologies for the creation of azo-ring structures and further functionalizable iodo components (path a).[14] In path b, although generation of iodo-enamines *via* intermolecular iodoamination of alkynes would be an alternative method for the contribution of enamines, it remains a highly challenging task, which may face the major hurdle that iodine would generate *N*-iodoamines in the present of amines rather than activate the alkynes.[15] Despite this, we assumed the type of the intermolecular iodoamination mentioned above would be achieved if active alkynes and suitable iodonium reagent were appropriately chosen. Over the past decade, ynamides have been established as the ultimate synthetic units because of their electron-rich and relatively stable nature.[16] And our group reported a rare *6-exo-dig* ring closure reaction of ynamides, in which we achieved an intermolecular iodocyclization of ynamides using acetonitrile as nitrogen nucleophile reagent.[17] More recently, Baell's group developed regio- and stereoselective iodoacyloxylations of alkynes and ynamides, by utilizing a combination of iodobenzene dicarboxylate and iodine as iodonium reagent.[18] Inspired by those results, we envisioned the possibility of the synthesis of enmines through an iodine-mediated intermolecular iodoamination of ynamides with amines. Following our ongoing efforts in exploring the reactivity of ynamides,[19] We herein report that intermolecular iodoamination of ynamides could be achieved under I_2/TBHP condition and this iodoamination revealed a rare entry to 1-diiodoenamines from terminal alkynes.



Scheme 1. Current achievements and challenges of iodoamination

In the initial experiments, reaction conditions were focused on optimizing a variety of reaction parameters by a model reaction between terminal ynamide (**1a**) and morpholine. First of all, different normal systems of active iodide ion, such as I_2/*tert*-butyl hydrope roxide (TBHP), KI/TBHP, Bu_4NI/TBHP, NIS, bis(2,4,6-collidine)iodonium hexafluorophosphate $[I(coll)_2 \cdot PF_6]$, were tested (Table 1, entries 1-5). We found that only I_2/TBHP exhibited the obvious reactivity, and desired intermolecular iodoamination product **2a** was isolated in 23% yield along with byproduct 1,2,2-triiodovinylamide **3a** in 43% yield. Other oxidants including H_2O_2, $PhI(OAc)_2$, Oxone, *m*-CPBA were subsequently tested, and none of them could promote this novel reaction (Table 1, entries 6-9). Besides no desired product **2a** was observed when the model reaction was carried out in the presence of I_2 without TBHP (Table 1, entry 10). Next, we screened the reaction in the presence of different solvents in order to further improve the yield of **2a**. When the

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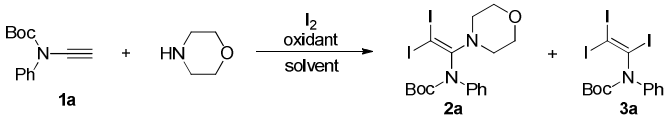
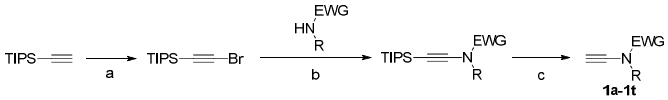
reaction performed in the presence of polar solvent, the desired product **2a** was afforded in poor yields while **3a** in moderate to good yield. To our delight, 61%-66% yield of **2a** was isolated when the model reaction was carried out in nonpolar solvent, such as benzene and toluene (Table 1, entries 18-19). Reduce the amount of morpholine form 3.0 to 2.0 equiv, the reaction could form the desired product **2a** but in lower yield (Table 1, entry 20). The effect of the loading of I_2 showed that 3.0 equiv of I_2 gave the lower yield (Table 1, entry 21). Last, the effect of TBHP loading showed that 3.0 equiv of TBHP gave the highest yield (71%) (Table 1, entries 22-23).

Table 1. Optimization of reaction conditions[a]



Entry	[I] (2.0 equiv)	Oxidant (equiv)	Solvent	Yield[b] **2a**/**3a**
1	NIS	--	DCM	nr
2	$I(coll)_2 \cdot PF_6$	--	DCM	nr
3	KI	aq.TBHP(2.0)	DCM	nr
4	Bu_4NI	aq.TBHP(2.0)	DCM	nr
5	I_2	aq.TBHP(2.0)	DCM	23/43
6	I_2	H_2O_2(2.0)	DCM	nr
7	I_2	Oxone(2.0)	DCM	nr
8	I_2	$PhI(OAc)_2$(2.0)	DCM	nr
9	I_2	*m*-CPBA(2.0)	DCM	nr
10	I_2	--	DCM	--/54
11	I_2	aq.TBHP(2.0)	DMF	--/--
12	I_2	aq.TBHP(2.0)	CH_3OH	--/51
13	I_2	aq.TBHP(2.0)	CH_3CN	--/52
14	I_2	aq.TBHP(2.0)	Dioxane	13/47
15	I_2	aq.TBHP(2.0)	THF	--/71
16	I_2	aq.TBHP(2.0)	EA	15/46
17	I_2	aq.TBHP(2.0)	DCE	24/51
18	I_2	aq.TBHP(2.0)	benzene	61/12
19	I_2	aq.TBHP(2.0)	toluene	66/9
20[c]	I_2	aq.TBHP(2.0)	toluene	59/14
21[d]	I_2	aq.TBHP(2.0)	toluene	53/19
22	I_2	aq.TBHP(3.0)	toluene	71/--
23	I_2	aq.TBHP(4.0)	toluene	64/--

[a] *Reaction conditions*: 1a (0.3 mmol), morpholine (3.0 equiv), I_2 (2.0 equiv), and aq. TBHP (2.0 equiv), in toluene (2.0 mL) at rt for 12 h; nr = No Reaction; aq. TBHP (70 % in H_2O) was used; H_2O_2 (30% in H2O) was used. [b] Isolated yield. [c] morpholine (2.0 equiv) was used. [d] I_2 (3.0 equiv) was used.

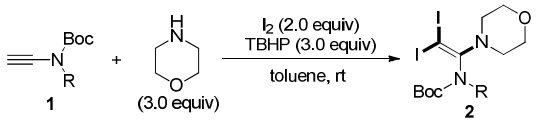


Scheme 2. Synthesis of terminal ynamides. a) NBS (1.25 equiv), $AgNO_3$ (5 mol%), acetone, rt; b) $CuSO_4 \cdot 5H_2O$ (5 mol%), 1,10-Phen (10 mol%), K_3PO_4 (2.0 equiv), toluene, 85 °C; c) TBAF (1.1 equiv), THF, 0 °C-rt.

We synthesized some terminal yanmides **1a-1t** to further examine the flexibility of this transition according to the previously reported methodology (Scheme 2).[20]

With the optimum reaction conditions in hand, we next examined the scope and generality of various ynamides in this transformation, and the results are summarized in Table 2. It is noteworthy that this reaction could be scaled up to 3.0 mmol in high yield with similar efficiency (Table 1, entry 1). And the structure of **2a** was further confirmed *via* single-crystal X-ray diffraction (For details, see ESI). Terminal ynamides with methyl on the *ortho*-position in the *N*-aryl ring were converted into the corresponding diiodo-enamide **2b** in acceptable yield (Table 2, entry 2). Ynamides with other groups, such as Me, F, Cl, Br, MeO and CF_3 substituted on the *meta*-position of the *N*-aryl ring were able to be converted into the corresponding diiodo-enamides in moderate to good yields, and ynamide with strongly electron-withdrawing group gave higher yield (Table 2, entries 5-8). Meanwhile, the *para*-effect was not obvious for methyl, bromo or chloro groups on the *para*-position of the *N*-aryl ring, and corresponding products in the reactions were obtained in 63-68% yields (Table 2, entries 9-11). Ynamides possessing 2-naphthyl, benzo[*d*][1,3]dioxol-5-yl and benzyl on the *N*-atom could also succeed in affording the desired oxazolidine-2,4-diones in 52-62% yields (Table 2, entries 12-15).

Table 2. I_2/TBHP mediated iodoamination of terminal ynamides[a]



Entry	R	Product	Isolated yield (%)
1	Ph	**2a**	71 73[b]
2	*o*-MePh	**2b**	34
3	*m*-MePh	**2c**	65
4	*m*-FPh	**2d**	69
5	*m*-ClPh	**2e**	70
6	*m*-BrPh	**2f**	72
7	*m*-MeOPh	**2g**	44
8	*m*-CF_3Ph	**2h**	76
9	*p*-MePh	**2i**	68
10	*p*-ClPh	**2j**	63
11	*p*-BrPh	**2k**	66
12	2-naphthyl	**2l**	62
13	benzo[*d*][1,3]dioxol-5-yl	**2m**	54
14	Bn	**2n**	52
15	*p*-MeOBn	**2o**	53

[a] *Reaction conditions*: 1 (0.3 mmol), morpholine (3.0 equiv), I_2 (2.0 equiv), and aq. TBHP (3.0 equiv), in toluene (2.0 mL) at rt for 12 h. [b] Scale-up experiment with 3.0 mmol **1a** loading.

Under the optimum conditions, we next explored the scope and limits of various ynamides and amines (Table 3). Ethyl ethynyl(phenyl)carbamate **1p** gave the corresponding product in 65% yield (Table 3, 2p). Terminal ynesulfonamides were also effective substrates, and their reactions provided the expected products **2q-2r** in moderate yields (Table 3, 2q-2r). Bearing *n*-butyl on the *N*-atom, terminal ynesulfonamides could also afford the product *N*-butyl-*N*-(2,2-diiodo-1-morpholinovinyl)-4-methylbenzenesulfonamide **2s** in 33% yield (Table 3, 2s). In addition, substituted indole was examined and could be transformed into the corresponding products in 78% yield (Table 3, 2t). By investing a range of amines, we found that the iodoamination also reacted with thiomorpholine and form product **2ab** in 74 % yield (Table 3, 2ab). *tert*-Butyl piperazine-1-carboxylate was employed in the reaction to give the corresponding diiodoenamide **2ac** in moderate yield (Table 3, 2ac). Although the reaction between **1a** and piperidine did work by checking in TLC, no corresponding diiodoenamides was isolated probably due to the unstable of product **2ad** (Table 3, 2ad). On the contrary, ester groups in the 4-position of the piperidine increased the reactivity of piperidine and achieved accepted yields of the diiodoenamides **2af** and **2ag** (Table 3, 2ae-2af).

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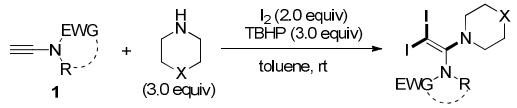
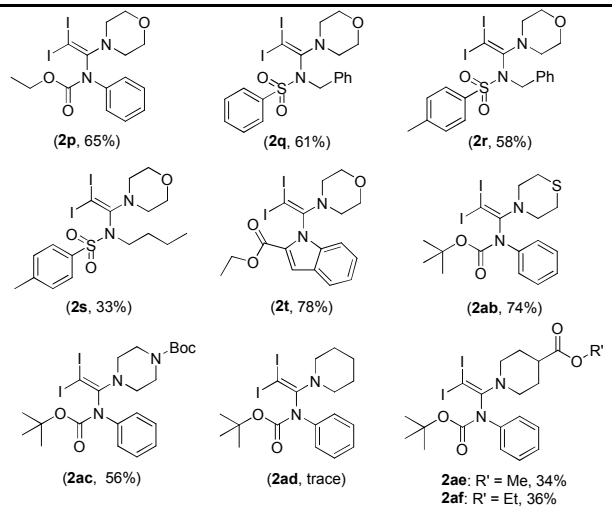
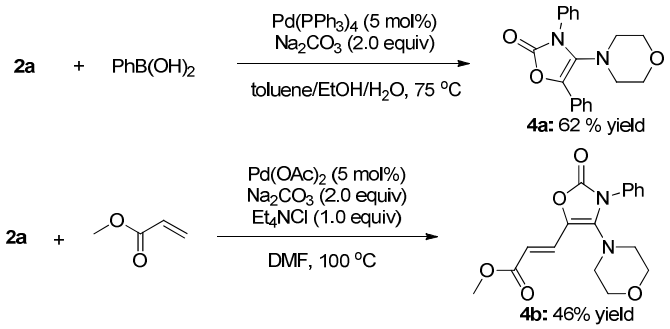
Table 3. I_2/TBHP mediated iodoamination of terminal ynamides





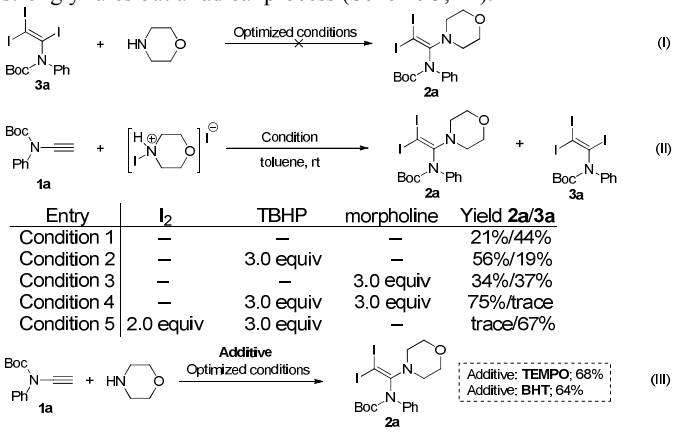
[a] *Reaction conditions*: 1 (0.3 mmol), morpholine (3.0 equiv), I_2 (2.0 equiv), and TBHP (3.0 equiv), in toluene (2.0 mL) at rt for 12 h.

Then, we started to investigate the synthetic utility of the 1-diiodoenmides obtained by our method. To our delight, we found that *tert*-butyl (2,2-diiodo-1-morpholinovinyl)carbamates was an ideal structure for the contribution of 3,4,5-multisubstituted oxazolones. For example, an interesting Suzuki-Miyaura cross-coupling/cyclization product 4-morpholino-3,5-diphenyloxazol-2(3*H*)-one **4a** was generated in 62% yield under general Suzuki condition. Similarly, **2a** could afford the Heck cross-coupling/cyclization product **4b** in moderate yield under general Heck condition.

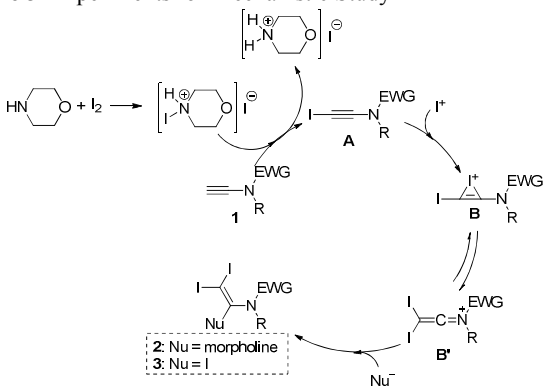


Scheme 3. Pd-catalyzed cross-coupling/cyclization of *tert*-butyl (2,2-diiodo-1-morpholinovinyl)carbamates.

To understand the mechanism of the reaction, several control experiments were performed. 1,2,2-triiodovinylamide **3a** could not produce **2a** under recommended reaction conditions, which indicated that the formation of C−N bond might be formed through a nucleophilic addition instead of nucleophilic substitution (Scheme 3, I). Generally, the reaction of iodine and morpholine normally affords *N*-iodomorpholine.[15] We further our examination to determine whether *N*-iodomorpholine plays any role in this novel transformation system. Thus *N*-iodomorpholine hydroiodide was synthesized and further investigated. Only 21% yield of **2a** was given in the reaction between *N*-iodomorpholine and ynmaides **1a** (Scheme 3, Condition 1), and a 56% yield was obtained when TBHP added (Scheme 3, Condition 2). The reaction also gave poor results only with addition of morpholine (Scheme 3, Condition 3). When morpholine and TBHP were added, a relatively higher yield of corresponding product **2a** was obtained (Scheme 3, Condition 4). When I_2 and TBHP were utilized for this reaction, the desired product **2a** could not be produced (Scheme 3, Condition 5). All the results above indicated that *N*-iodomorpholine is the important iodonium reagent rather than I_2. We also confirmed that the iodoamination proceeded smoothly to form *tert*-butyl (2,2-diiodo-1-morpholinovinyl)(phenyl)carbamate **2a** in 64-68% yields in the presence of radical scavengers like TEMPO and BHT, which strongly rules out a radical process (Scheme 3, III).



Scheme 3. Experiments for Mechanistic Study



Scheme 4. Proposed mechanism for the iodoamination of terminal ynamides.

Although the exact mechanism of this reaction and the actual role of TBHP in this transition cyclization have not been very clear so far, a possible tandem reaction pathway was proposed on the basis of our experimental data above and reported literatures, as shown in **Scheme 4**. When treated with *N*-iodomorpholine generated from the reaction of I_2 with morpholine, terminal ynmaides can produce the corresponding 1-iodoynamides intermediate **A**.[8a, 15b] And in the presence of I^+ as a weak Lewis acid, **A** can next produce iodonium intermediate **B**, which is also characterized by keteniminium forms **B′** to increase their electrophilicity and regioselectivity.[16] Finally, **B′** undergoes a nucleophilic attack by morpholine[21] or iodide anion to produce 1-diiodoenmides **2** or byproduct 1,2,2-triiodovinylamides **3**.[22] Probably due to oxidizability of TBHP, iodide anion would be oxidized decreasing the generation of byproducts **3**.[23]

Conclusions

In summary, we have developed a novel and efficient protocol for the synthesis of *α*-amino-*β*,*β*-diiodo-enamides by I_2/TBHP mediated

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intermolecular iodoamination. This method not only comprehensively reported an intermolecular iodomination of alkynes to diiodoenamines for the first time, but also tolerated a wide range of functional groups on the ynamides component under mild condition. Mechanistic study revealed that *N*-iodomorpholine plays a key role in the transition cycle. And the *tert*-butyl (2,2-diiodo-1-morpholinovinyl) carbamates have the potential to be converted to various 3,4,5-multisubstituted oxazolones by Pd-catalyzed cross-coupling/cyclization. Further studies on iodine-mediated C-C, C-N, and C-O bond formations of ynamides are being conducted in our laboratory and will be reported in due course.

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Notes and references

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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