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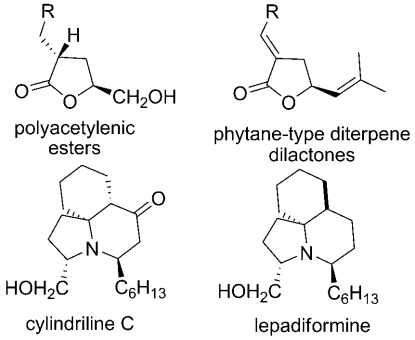
A Novel Iodine-Promoted Tandem Cyclization: An Efficient Synthesis of Substituted 3,4-Diiodoheterocyclic Compounds

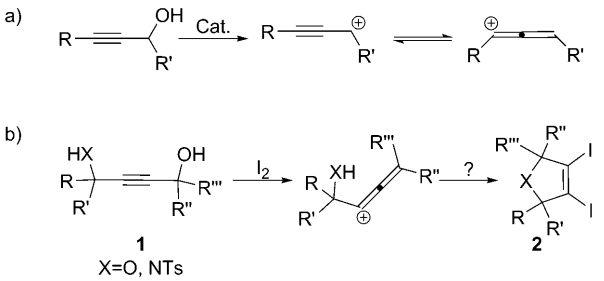
Ke-Gong Ji, Hai-Tao Zhu, Fang Yang, Xing-Zhong Shu, Shu-Chun Zhao, Xue-Yuan Liu, Ali Shaukat, and Yong-Min Liang*[a]

Five- and six-membered heterocyclic rings occur as key structural subunits in numerous natural products, such as polyacetylenic esters,[1] phytane-type diterpenedilactones,[2] cylindriline C, and lepadiformine.[3] Thus, the development of novel methods for the annulation of five- and six-membered heterocyclic rings is necessary, including metal-free, mild, environmentally friendly, and atom-economic conditions.



Recently, the electrophilic cyclization of heteroatomic nucleophiles, such as oxygen, nitrogen, and sulfur, with alkynes has proven to be an effective method for the synthesis of these heterocyclic compounds.[4–13] Due to the excellent alkynophilicity of molecular iodine, much attention has been paid to iodine-based alkyne activation as an attractive protocol for developing new and efficient iodocyclizations.[6–8] Many important heterocycles, such as benzo[*b*]thiophenes,[4] benzofurans,[5] 2,3-dihydropyrroles,[6] pyrroles,[6] furans,[7] indoles,[8] isochromenes,[9] isocoumarins,[10] α-pyrones,[10] isoquinolines,[11] quinolines,[11] isoxazoles,[12] and oxazoles,[13] have syntheses based on this strategy. Thus, electrophilic cyclization reactions continue to be an area of active research in the field of synthetic chemistry.

In the context of our ongoing efforts to construct functionalized heterocyclic structures,[14] we have found that propargyl carbocations,[15] which may be in equilibrium with allene cations (Scheme 1a), are perfect intermediates for a



Scheme 1. a) Possible equilibrium. b) Design of the domino process.

domino process. We envisioned that this type of propargyl alcohol (**1**) could undergo the isomerization process in the presence of I_2 and then cyclize to give 3,4-diiodoheterocyclic compounds **2** (Scheme 1b). Herein, we report example reactions of but-2-yne-1,4-diol and 4-aminobut-2-yn-1-ol derivatives towards the synthesis of 3,4-diiodoheterocyclic compounds in the presence of I_2. In this reaction, both the iodine anion and cation generated from I_2 are used effectively.

Initially, we used 1-phenylbut-2-yne-1,4-diol (**1a**; 0.3 mmol) and I_2 (1.2 equiv) in CH_2Cl_2 (3 mL) at room temperature; to our delight, the desired product, 3,4-diiodo-2-phenyl-2,5-dihydrofuran (**2a**) was isolated in 62% yield, after 12 h (Table 1, entry 1). On increasing the amount of I_2

[a] Dr. K.-G. Ji, H.-T. Zhu, F. Yang, X.-Z. Shu, S.-C. Zhao, X.-Y. Liu, A. Shaukat, Prof. Dr. Y.-M. Liang
State Key Laboratory of Applied Organic Chemistry
Lanzhou University
Lanzhou 730000 (China)
Fax: (+86) 931-8912582
E-mail: liangym@lzu.edu.cn

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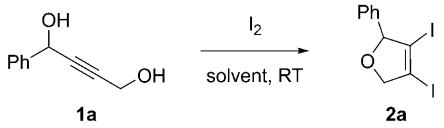
Table 1. Optimization of the iodine cyclization of 1-phenylbut-2-yne-1,4-diol, **1a**.[a]



1a **2a**

Entry	Solvent	I_2 [equiv]	Time [h]	Yield [%][b]
1	CH_2Cl_2	1.2	12	62
2	CH_2Cl_2	1.5	8	95
3	CH_2Cl_2	2.0	4	99
4	dry CH_2Cl_2	2.0	12	trace
5	DCE	2.0	6	90
6	DMF	2.0	12	nr[c]
7	MeOH	2.0	12	nr[c]
8	THF	2.0	12	41
9	CH_3CN	2.0	12	72

[a] Conditions: **1a** (0.3 mmol) and I_2 in CH_2Cl_2 (3.0 mL), at room temperature. [b] Isolated yield. [c] nr = no reaction.

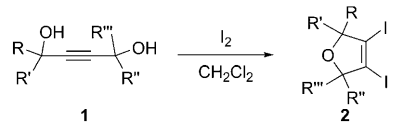
present to 1.5 equivalents, a 95% yield of **2a** was obtained after 8 h (Table 1, entry 2) and, on further increasing the amount of I_2 to 2.0 equivalents, an excellent yield of **2a** was obtained (up to 99%; Table 1, entry 3). The reaction was also tested in dry CH_2Cl_2, in which case only trace amounts of **2a** were observed (Table 1, entry 4).

The reaction was also tested in other solvents. The use of dichloroethene (DCE) gave an almost identical result, albeit with a very slightly lower yield (Table 1, entry 5), whereas DMF and MeOH proved to be ineffective and THF and CH_3CN were less effective (Table 1, entries 6–9). Thus, the optimum reaction conditions employ 1.0 equivalent of **1a** and 2.0 equivalents of I_2, in CH_2Cl_2, at room temperature.

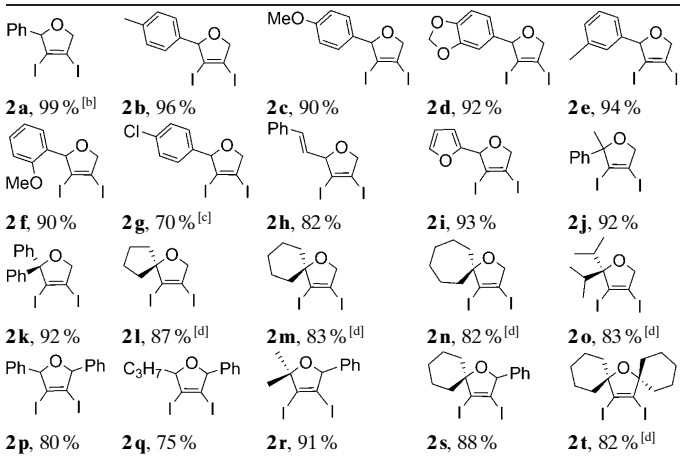
With the optimized conditions in hand, various but-2-yne-1,4-diol derivatives, **1a–t**, were subjected to the above conditions, as depicted in Table 2. Thus, the tandem carbon–heteroatom bond formation reactions of but-2-yne-1,4-diol derivatives **1a–t** proceeded smoothly to provide the corresponding products **2a–t** in moderate to excellent yields. The reaction works well with aromatic R′ groups. Electron-rich aryl groups showed better results than those with an electron-withdrawing group in this tandem reaction (e.g., **1a** vs. **1g**). Substrates **1h** and **1i**, with a styrene or heteroaromatic R′ group, can also afford the desired products **2h** and **2i** in 83 and 93% yield, respectively. Interestingly, substrates like **1l–o**, with aliphatic groups, can also gave the corresponding 3,4-diiodoheterocyclic compounds **2l–o** in moderate yields. Other substrates, like **1p–t**, can also afford the corresponding products **2p–t** in moderate to excellent yield.

Furthermore, to expand the scope of this reaction, we also investigated a range of 4-aminobut-2-yn-1-ol derivatives, **1u–ac**. It was found that, under the optimized conditions, substrates **1u–ac** were transferred into 3,4-diiodo-dihydropyrroles **2u–ac** in moderate to excellent yields, as depicted in Table 3. The molecular structure of the representative product **2u** was determined by X-ray crystallography (Figure 1).[16] Substrates like **1x–ac**, with aliphatic substituents, can also afford the desired spiro products in good yield.

Table 2. Synthesis of 3,4-diiododihydrofurans **2** from but-2-yne-1,4-diol derivatives **1**.[a]

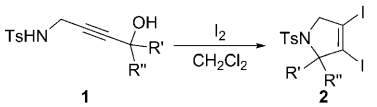


1 **2**

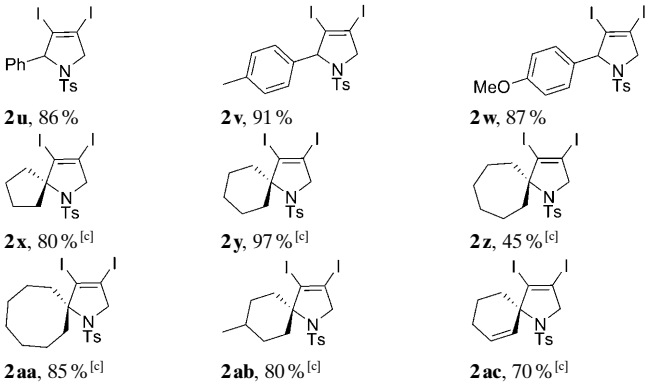


[a] All reactions were run under the following conditions, unless otherwise indicated: **1** (0.30 mmol) and I_2 (2.0 equiv) in CH_2Cl_2 (3 mL), at room temperature. [b] Isolated yield. [c] 20% of the starting material was recovered. [d] The reaction was carried out at 40 °C.

Table 3. Synthesis of 3,4-diiododihydropyrroles **2u–ac**[b] from 4-aminobut-2-yn-1-ol derivatives **1u–ac**.[a]



1 **2**



[a] All reactions were run under the following conditions, unless otherwise indicated: **1** (0.30 mmol) and I_2 (3.0 equiv) in CH_2Cl_2 (3 mL), at room temperature. [b] Isolated yield. [c] The reaction was carried out at 40 °C.

As we know, six-membered pyran rings are very important in organic chemistry. Consequently, under the optimized conditions, we also investigated the reaction of pent-2-yne-1,5-diol derivative **1ad**. Fortuitously, 4,5-diiodo-2,6-di-

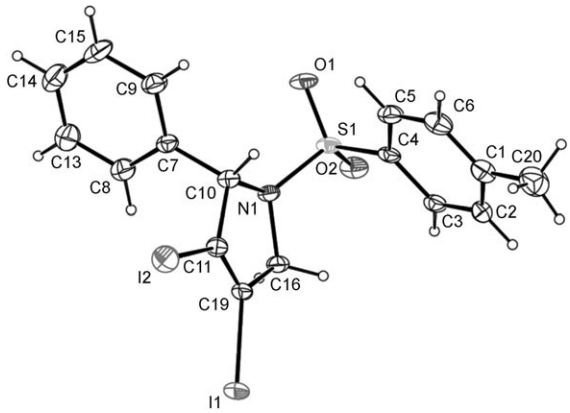
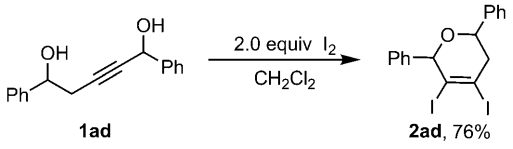


Figure 1. X-ray crystal structure of **2u**.[16]

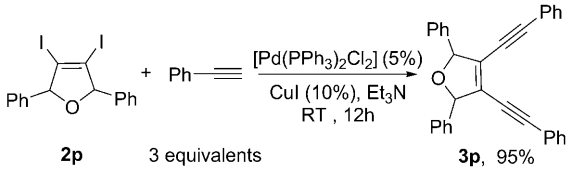
phenyl-3,6-dihydro-2*H*-pyran (**2ad**) was obtained in moderate yield (Scheme 2).

A standard feature of this process is that the diiodoheterocyclic compounds produced by the iodocyclization can be



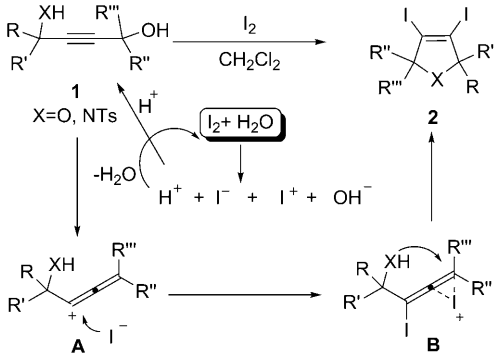
Scheme 2. Synthesis of 4,5-diiodo-2,6-diphenyl-3,6-dihydro-2*H*-pyran (**2ad**).

further elaborated by using various palladium-catalyzed processes. For example, the Sonogashira coupling[17] of 3,4-diiododihydrofuran **2p** affords the corresponding product **3p** in excellent yield (Scheme 3).



Scheme 3. An example of further elaboration of compounds **2**.

On the basis of the observations above, we propose the following mechanism for this iodine cyclization (Scheme 4). In the CH_2Cl_2 used, trace amounts of water react with the I_2 to produce protons, iodine anions, iodine cations, and hydroxide anions. In the presence of protons, substrate **1** loses a hydroxide group to afford the intermediate allene cation **A**. The iodine anion, generated from I_2, then attacks allene cation **A** to give allene **B**, which coordinates to the iodine cation to generate an iodonium intermediate. This is followed by intramolecular attack of the heteroatom on the activated allene[18] to afford the cyclized product **2**. For this reaction, trace amounts of water are recycled and necessary.



Scheme 4. Proposed mechanism.

In conclusion, an efficient synthesis of highly substituted 3,4-diiodoheterocyclic compounds from but-2-yne-1,4-diol and 4-aminobut-2-yn-1-ol derivatives has been developed. In this reaction, trace amounts of water are necessary and both the iodine anion and cation, generated from I_2, are used effectively.

Experimental Section

General procedure–Synthesis of diiodoheterocyclic derivatives: I_2 (152.4 mg, 0.6 mmol, 2 equiv) was added to a solution of **1** (0.30 mmol) in wet CH_2Cl_2 (3.0 mL) and the resulting mixture was stirred at room temperature. When the reaction was considered complete, as determined by TLC analysis, the reaction mixture was diluted with diethyl ether (40 mL), washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford the corresponding diiodoheterocyclic compound **2**.

Acknowledgements

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Keywords: allenes · cyclization · heterocycles · iodine · propargyl carbocations

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