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Facile Synthesis of Halogenated Spiroketals via a Tandem Iodocyclization

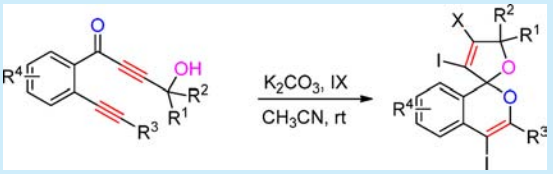
Jia Wang,[†] Hai-Tao Zhu,[†] Ying-Xiu Li,[†] Li-Jing Wang,[†] Yi-Feng Qiu,[†] Zi-Hang Qiu,[†] Mei-jin Zhong,[†] Xue-Yuan Liu,[†] and Yong-Min Liang*[,†,‡]

[†]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P.R. China

[‡]State Key Laboratory of Solid Lubrication, Lanzhou Institute of Chemical Physics, Chinese Academy of Science, Lanzhou, 730000, P.R. China

Supporting Information

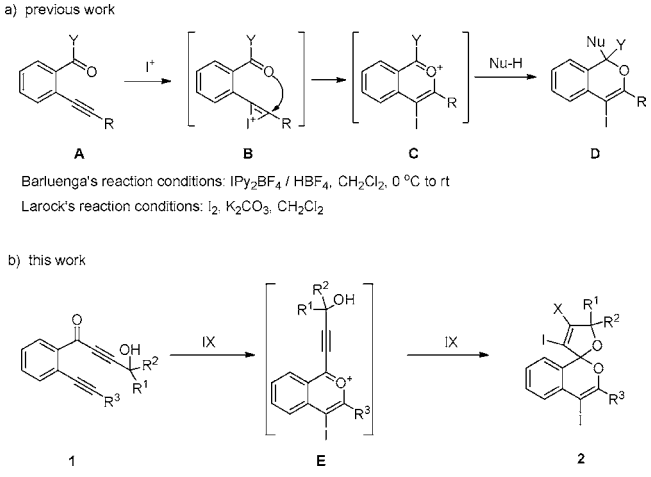
ABSTRACT: A strategy for the synthesis of spiroketal compounds through a tandem iodocyclization of 1-(2-ethynylphenyl)-4-hydroxybut-2-yn-1-one derivatives is presented. This reaction could proceed under very mild conditions in a short time and avoid the use of expensive and toxic metal catalysts. Moreover, the resulting halides can be further exploited by subsequent palladium-catalyzed coupling reactions, which act as the important intermediates for building other valuable compounds.



Excellent alkynophilicity of iodine cations as reactive intermediates has been proven to be one of the most interesting subjects in organic chemistry[1] and has been widely used for the preparation of iodocyclization.[2] Indeed, a series of intramolecular iodine-induced cyclization reactions of carbon-centered or heteroatom nucleophiles with alkynes have been reported to construct carbocycles[3] and heterocycles.[4] Nevertheless, only a few examples of sequential tandem iodospiroketalization of alkynes have been reported until now.[5] Furthermore, spiroketals are ubiquitous structural units in numerous biologically significant natural products,[6] which essentially contribute to bioactivity and represent a privileged scaffold in drug discovery.[7] As a result of their remarkable and diverse biological activities,[8] spiroketals have been the focus of considerable attention for synthetic organic chemists as well as pharmaceutical chemists.[9] Thus, much attention has been given to the development of new methods for the synthesis of spiroketals. However, many traditional approaches to spiroketals are still limited to metal-mediated[10] or acid-catalyzed[11] strategies. Therefore, seeking alternative methods for the construction of spiroketals is indeed desirable.

In 2003, the Barluenga group described an interesting transformation of *o*-alkynyl aldehydes with intermolecular nucleophiles to iodoisochromenes utilizing bis(pyridine) iodonium tetrafluoroborate (IPy_2BF_4)[12] (Scheme 1a). Afterward, Larock and co-workers reported another analogous electrophilic cyclization promoted by molecular iodine.[13] These reactions are generally believed to proceed through a stepwise mechanism. In the presence of I_2, the oxygen of the carbonyl group attacks the alkyne group activated by the iodine cation to form the intermediate **C**, which is immediately trapped by the nucleophile to give the product **D**. Encouraged by these achievements and in the context of our ongoing interest to the electrophilic cyclization of alkynols,[14] we envisioned that the substrates **1** containing propargylic alcohol could undergo the cyclization of the carbonyl group to form the intermediate **E** with an alkynol moiety, which could tandemly cyclize to give the halogenated spiroketals **2** (Scheme 1b). Herein, we report a concise and effective method for the synthesis of a variety of spiroketals via sequential tandem iodocyclization.

Scheme 1. Electrophilic Ketalization



At the onset of our investigation, we examined the reaction of 4-hydroxy-1-(2-((4-methoxyphenyl)ethynyl)phenyl)-4-methylpent-2-yn-1-one (**1a**) with 2 equiv of I_2 in CH_3CN at room temperature. To our delight, the desired product 3,4,4′-triiodo-3′-(4-methoxyphenyl)-5,5-dimethyl-5*H*-spiro[furan-2,1′-isochromene] (**2a**) was isolated in 57% yield after 0.5 h

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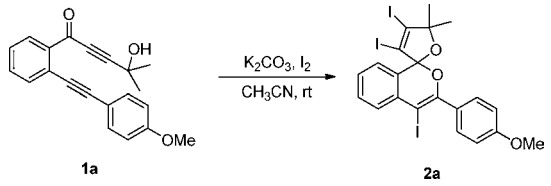
(Table 1, entry 1). An increase in the amount of I_2 to 3 equiv afforded **2a** in 87% yield. However, further increasing the amount of I_2 (3.5 equiv) gave a slightly lower yield of **2a** (entry 3). After screening a series of bases, such as K_2CO_3, Na_2CO_3, K_3PO_4, and KOH, we found that K_2CO_3 was the best compared with the others (entries 2 and 4−6). In the meantime, the study of solvent influence showed that none of CH_2Cl_2, THF, CH_3COCH_3, and CH_3NO_2 could give a superior yield (entries 7−10). In adition, prolonging the reaction did not provide a better result (entry 11). With a series of detailed investigations mentioned above, the combination of 1.0 equiv of **1a**, 3.0 equiv of I_2, and 1.0 equiv of K_2CO_3 in CH_3CN at room temperature are the optimum reaction conditions.

Table 1. Optimization of the Electrophilic Spiroketalization of 4-Hydroxy-1-(2-((4-methoxyphenyl)ethynyl)phenyl)-4-methylpent-2-yn-1-one[a]



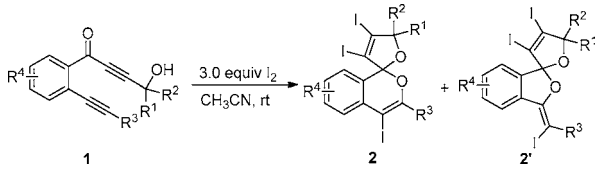
1a **2a**

entry	solvent	I_2 (equiv)	base (1.0 equiv)	time (h)	yield[b] (%)
1	CH_3CN	2.0	K_2CO_3	0.5	57
2	**CH_3CN**	**3.0**	**K_2CO_3**	**0.5**	**87**
3	CH_3CN	3.5	K_2CO_3	0.5	83
4	CH_3CN	3.0	Na_2CO_3	0.5	85
5	CH_3CN	3.0	K_3PO_4	0.5	84
6	CH_3CN	3.0	KOH	0.5	65
7	CH_2Cl_2	3.0	K_2CO_3	0.5	83
8	THF	3.0	K_2CO_3	0.5	84
9	CH_3COCH_3	3.0	K_2CO_3	0.5	52
10	CH_3NO_2	3.0	K_2CO_3	0.5	46
11	CH_3CN	3.0	K_2CO_3	1.0	86

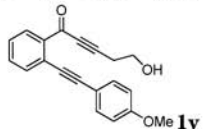
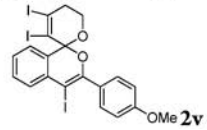
[a]All reactions were run under the following conditions, unless otherwise indicated: 0.20 mmol of **1a**, 3.0 equiv of I_2, and 1.0 equiv of base in 4 mL of solvent were stirred at room temperature. [b]Yield of isolated product.

After having established the optimized conditions for the present reaction, various 1-(2-ethynylphenyl)-4-hydroxybut-2-yn-1-one derivatives were subjected to the above conditions, as summarized in Table 2. The reactions of substrates **1a** and **1b** bearing electron-donating aromatic groups (R^2) at the alkynyl carbon resulted in the corresponding products **2a** and **2b** in excellent yields, respectively. The structure of the representative product **2a** was determined by X-ray crystallographic analysis. Unexpectedly, under the optimized conditions, the desired products **2c** and **2f** appeared along with the byproducts **2′c** and **2′f** (entries 3 and 6). Meanwhile, the proportion of products **2c** and **2f** decreased with the increase of electronegativity on the substituent R^3 group (entry 3 vs 6). Surprisingly, in the case of 4-$NO_2C_6H_4$-substituted substrate **1g**, the reaction gave a sole 5-*exo-dig* cyclization product **2′g**, rather than the six-membered ring (entry 7). Fortunately, the presence of aliphatic group of pentyl on R^3 in substrate **1d** was also tolerated, and the desired product **2d** was obtained in 75% yield (entry 4). However, the substrate **1e** only led to **2e** in 36% yield. This might be due to the weak nucleophilicity of the aliphatic acetylene. The reactions also worked well with the substrates **1h−l** with

Table 2. Synthesis of Triiodinated Spiroketals 2 and 2′[a]



1 **2** **2′**

entry	substrate (R^1, R^2, R^3, R^4)	product	yield[b] (%)
1	$R^1 = R^2 =$ Me, $R^3 = p$-OMePh, $R^4 =$ H	**2a**	87
2	$R^1 = R^2 =$ Me, $R^3 = p$-MePh, $R^4 =$ H	**2b**	86
3	$R^1 = R^2 =$ Me, $R^3 =$ Ph, $R^4 =$ H	**2c/2′c = 3.5/1.0**	70
4	$R^1 = R^2 =$ Me, $R^3 =$ Pentyl, $R^4 =$ H	**2d**	75
5	$R^1 = R^2 =$ Me, $R^3 =$ Cyclohex-1-en-1-yl, $R^4 =$ H	**2e**	36
6	$R^1 = R^2 =$ Me, $R^3 = p$-ClPh, $R^4 =$ H	**2f/2′f = 1.7/1.0**	68
7	$R^1 = R^2 =$ Me, $R^3 = p$-NO_2Ph, $R^4 =$ H	**2′g**	38
8	$R^1 = R^2 =$ Me, $R^3 = p$-OMePh, $R^4 =$ 5-Cl	**2h**	81
9	$R^1 = R^2 =$ Me, $R^3 = p$-OMePh, $R^4 =$ 4-Cl	**2i**	79
10	$R^1 = R^2 =$ Me, $R^3 = p$-OMePh, $R^4 =$ 5-Me	**2j**	87
11	$R^1 = R^2 =$ Me, $R^3 = p$-OMePh, $R^4 =$ 5-OMe	**2k**	61
12	$R^1 = R^2 =$ Me, $R^3 = p$-OMePh, $R^4 =$ 4,5-Dimethoxyl	**2l**	51
13	$R^1 = R^2 =$ Bu, $R^3 = p$-OMePh, $R^4 =$ H	**2m**	86
14	$R^1 = R^2 =$ Ph, $R^3 = p$-OMePh, $R^4 =$ H	**2n**	68
15	$R^1 = R^2 =$ Bn, $R^3 = p$-OMePh, $R^4 =$ H	**2o**	89
16	$R^1 = R^2 = p$-FPh, $R^3 = p$-OMePh, $R^4 =$ H	**2p**	62
17	$R^1 = R^2 = R^3 = p$-OMePh, $R^4 =$ H	**2q**	69
18	$R^1 = R^2 = -(CH_2)_5-$, $R^3 = p$-OMePh, $R^4 =$ H	**2r**	80
19	$R^1 = R^2 = -(CH_2)_6-$, $R^3 = p$-OMePh, $R^4 =$ H	**2s**	73
20	$R^1 = R^2 = -(CH_2)_7-$, $R^3 = p$-OMePh, $R^4 =$ H	**2t**	85
21	$R^1 = R^2 =$ H, $R^3 = p$-OMePh, $R^4 =$ H	**2u**	63
22	 **1v**  **2v**		65

[a]All reactions were run under the following conditions, unless otherwise indicated: 0.2 mmol of **1** with 3.0 equiv of I_2 and 1.0 equiv of K_2CO_3 in 4 mL of CH_3CN at room temperature. [b]Isolated yields.

electron-donating or electron-withdrawing substituents on R^4, furnishing the expected products **2h−l** in good yields. Remarkably, the electron-withdrawing substituents on the C-4 or C-5 position gave better yields than the electron-donating ones (entries 8−12). This might be because the electron-withdrawing substituents increased the activity of the alkyne group. Subsequently, we examined the effect of substituents at R^1 and R^2. In contrast, the substrates **1n**, **1p**, and **1q** underwent the cyclization to give the products in low yields, which might

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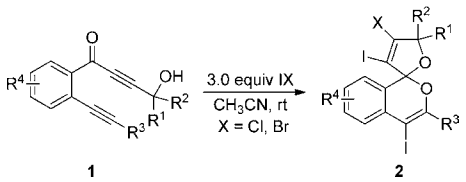
be due to the steric hindrance (entries 14, 16, and 17). It is noteworthy that when the R^1 or R^2 changed to the cyclic substituent, the corresponding products **2r–t** were obtained in good yields (entries 18–20). In addition, substrate **1v** with a butynol group gave the six-membered heterocyclic ring product **2v** in 65% yield (entry 22).

To explore the scope of the iodine-containing electrophiles as well as the mechanism of this electrophilic spiroketalization, the reactions of 1-(2-ethynylphenyl)-4-hydroxybut-2-yn-1-one derivatives with ICl and IBr were studied under the standard reaction conditions, as depicted in Table 3. The product **2aa**

Table 3. Synthesis of Diiodinated Spiroketals with ICl and IBr[a]



1 2

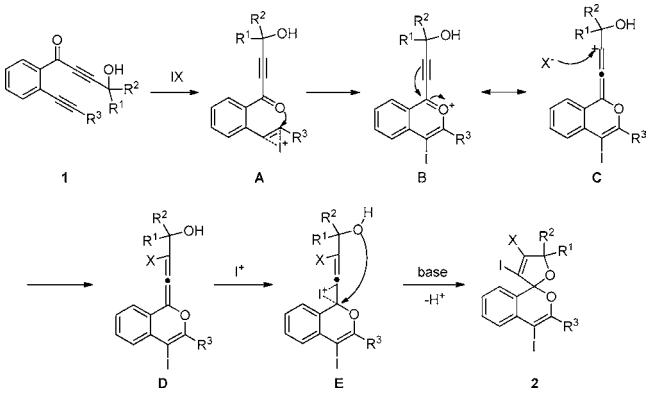
entry	1	IX	product	yield[b] (%)
1	**1a**	ICl	**2aa**	63
2	**1b**	ICl	**2ba**	83
3	**1h**	ICl	**2ha**	70
4	**1j**	ICl	**2ja**	60
5	**1m**	ICl	**2ma**	92
6	**1o**	ICl	**2oa**	80
7	**1r**	ICl	**2ra**	73
8	**1b**	IBr	**2bb**	76
9	**1j**	IBr	**2jb**	60
10	**1o**	IBr	**2ob**	43

[a]All reactions were run under the following conditions, unless otherwise indicated: 0.2 mmol of **1** with 3.0 equiv of IX and 1.0 equiv of K_2CO_3 in 4 mL of CH_3CN at room temperature. [b]Isolated yields.

was achieved in 63% yield (Table 3, entry 1). The structure of the representative product **2aa** was determined by X-ray crystallographic analysis. Similarly, other typical substrates also gave the corresponding chlorine-containing products in good yields (Table 3, entries 2–7). Meanwhile, in the presence of IBr, the desired products **2bb**, **2ob**, and **2jb** were gained in moderate to good yields (Table 3, entries 8–10).

On the basis of the above observations, a possible mechanism is outlined in Scheme 2. The alkyne moiety was first activated by iodide cation, and the oxygen of carbonyl group attacked the

Scheme 2. Proposed Reaction Mechanism

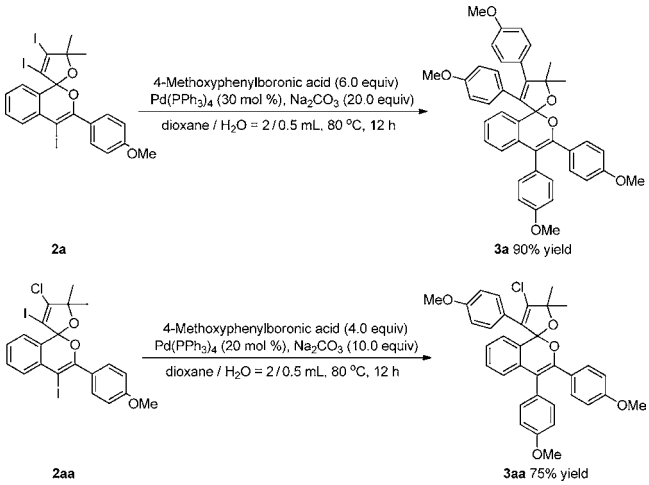


1 A B C D E 2

reactive species **A** to give the intermediate **B**, which could resonate with allene carbocation **C**. At the same time, the halogen anion captured the allene carbocation to give the halogenated intermediate **D**. Meanwhile, the intermediate **D** coordinated with the excess iodide cation to gain the complex **E**, which was attacked by the hydroxyl group and then released the hydrogen cation in the presence of base to attain the desired product **2**.

As shown in Scheme 3, spiroketal compounds **2a** and **2aa** can be further elaborated by using the Suzuki palladium-

Scheme 3. Palladium-Catalyzed Coupling Reactions



2a **3a** 90% yield

2aa **3aa** 75% yield

catalyzed processes.[15] The Suzuki coupling of **2a** and **2aa** afforded the corresponding products **3a** and **3aa** in 90% and 75% yields, respectively.

In conclusion, a new and mild protocol for the synthesis of halogenated spiroketals has been established. This method adds interest to this clean process and also relates to the incorporation of iodine. Foremost, the resulting halogenated spiroketals are readily elaborated to more products by using known organopalladium chemistry which may be essential intermediates for the synthesis of natural products. Further studies on the synthesis of spiroketal compounds are underway.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liangym@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

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