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Facile synthesis of 3,4-dihalofurans *via* electrophilic iodocyclization†

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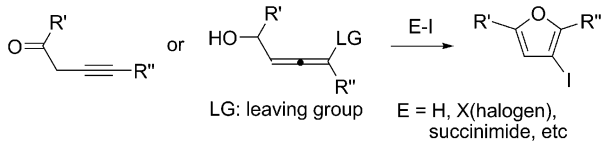
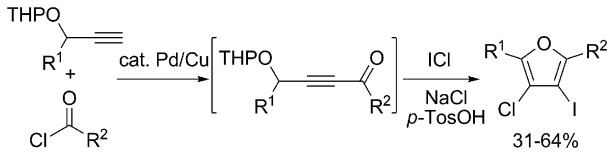
A facile, efficient, and general synthetic method for 3,4-dihalofurans has been developed *via* the electrophilic iodocyclization of various 4-hydroxy-2-but-2-yn-1-ones. The use of MeOH as a solvent is crucial for the efficient chemoselective synthesis of the corresponding 3,4-dihalofurans.

Polysubstituted furans are of great interest as natural products as well as synthetic building blocks.[1] Owing to their wide applications, the synthetic method for furans has been intensively developed.[1] Electrophilic iodocyclization of alkyne or allene bound substrates is one of the most efficient strategies for the construction of furans having a β-iodo-substituent under very mild conditions (eqn (1)).[2] Furthermore, the resulting iodine-containing products can be readily converted to the structurally elaborated polysubstituted furans regioselectively using transition metal-catalyzed coupling reactions. On the other hand, electrophilic iodocyclization for the synthesis of the dihalogenated furans has been rarely reported,[2h,3,4] although it provides an opportunity to produce the β,β′-disubstituted furans. Recently, Müller and co-workers reported a facile one-pot three-component reaction for the synthesis of 3-chloro-4-iodofurans with moderate yields (eqn (2)).[2h] However, it seems to be difficult to carry out the cross-coupling reaction of the two C–X bonds of the resulting furans, since C–Cl bonds generally exhibit low reactivity toward transition metal-catalyzed reactions. Therefore, the development of an efficient and general approach to iodo- or bromo-substituted dihalofurans is desirable. Herein, we wish to report a facile, efficient and general synthetic method for 3,4-dihalofurans **2** (X = Br, I) from 4-hydroxy-but-2-yn-1-ones **1** (eqn (3)).



(1)



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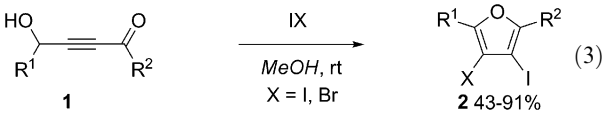

(3)

In continuation of our interest in the development of efficient synthetic methods of heterocycles,[5] and in iodocyclization chemistry,[6] we attempted to synthesize 3,4-diiodofurans through a simple iodine mediated electrophilic cyclization. However, when 4-hydroxy-1,4-diphenylbut-2-yn-1-one **1a** was treated with I_2 under the ordinary conditions, a mixture of the corresponding furan **2a** and the diiodinated acyclic olefin **3a** was obtained (Table 1, entry 1). This is not a surprising result, since the addition of I_2 to a triple bond takes place rather easily. We thought that the coexistence of a protic source may produce the corresponding diiodofuran **2a** selectively without formation of **3a**, because the presence of *p*-TosOH might be key for eqn (2).

The use of CH_2Cl_2 with proton sources, such as H_2O and TfOH, did not improve the yield of **2a** (entries 2 and 3). The presence of MeOH (1.0 equiv.) slightly improved the yield of **2a** (entry 4). The use of other aprotic solvents, such as THF, CH_3NO_2, $CHCl_3$, CCl_4, and benzene, did not increase the selectivity (entries 5–9). Fortunately, when MeOH or EtOH was used as a solvent, the yield of **2a** was dramatically increased and formation of **3a** was not detected (entries 10 and 11). These results indicate that such aprotic solvents are indispensable for the selective formation of **2a**.

The scope and limitations of iodine mediated electrophilic cyclization of various substituted 4-hydroxy-but-2-yn-1-ones are summarized in Table 2. The reactions of 4-hydroxy-4-phenylbut-2-yn-1-ones **1b** and **1c** bearing an electron-donating and an electron-withdrawing aromatic group at R^2 produced the corresponding diiodofurans **2b** and **2c** in 83% and 91% yields, respectively (entries 1 and 2). Not only a naphthyl substituent (**1d**), but also a tosyl-protected pyrrolyl (**1e**) group at R^2 afforded the desired products in good to high yields (entries 3 and 4). The reaction also worked well with the substrate **1f** having an alkyl substituent at R^2, furnishing the expected tetrasubstituted diiodofuran **2f** in good yield (entry 5).

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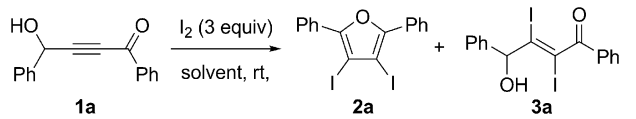
Table 1 Optimization of reaction conditions[a]

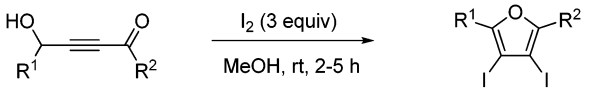


1a **2a** **3a**

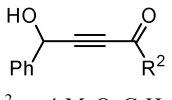
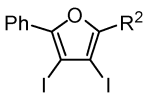
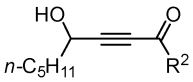
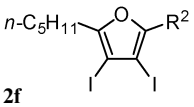
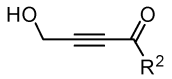
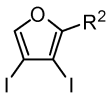
Entry	Solvent	Additive/ equiv.	Time/h	**2a**, Yield[b] (%)	**3a**, Yield[b] (%)
1	CH_2Cl_2		0.5	45	50
2	CH_2Cl_2	H_2O (0.5)	0.25	40	60
3	CH_2Cl_2	TfOH (0.1)	0.5	38	14
4	CH_2Cl_2	MeOH (1.0)	3	65	30
5	THF		3	21	69
6	CH_3NO_2		3	45	49
7	$CHCl_3$		1	41	58
8	CCl_4		0.25	43	55
9	Benzene		0.3	30	70
10	MeOH		5	96 (87)	0
11	EtOH		5	92	0

[a] Reaction conditions: **1a** (0.2 mmol), I_2 (0.6 mmol), anhydrous solvent (0.1 M), room temperature. [b] ^{1}H NMR yield determined using CH_2Br_2 as an internal standard. Isolated yield is shown in parentheses.

Table 2 Synthesis of 3,4-diiodofurans by electrophilic iodocyclization[a]



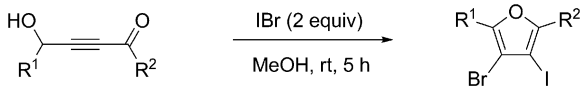
1 **2**

Entry	Substrates **1**	Products **2**	Yield[b] (%)
			
1	**1b** R^2 = 4-MeO–C_6H_4	**2b**	83
2	**1c** R^2 = 4-Cl–C_6H_4	**2c**	91
3	**1d** R^2 = 1-naphthyl	**2d**	81
4	**1e** R^2 = 2-(1-tosyl)pyrrolyl	**2e**	43
5	**1f** R^2 = n-C_5H_{11}	**2f**	63
			
6	**1g** R^2 = Ph	**2f**	89
7	**1h** R^2 = 4-MeO–C_6H_4	**2h**	80
8	**1i** R^2 = 4-Cl–C_6H_4	**2i**	88
9	**1j** R^2 = 1-naphthyl	**2j**	75
10	**1k** R^2 = n-C_5H_{11}	**2k**	68
			
11	**1l** R^2 = Ph	**2l**	85
12	**1m** R^2 = n-C_5H_{11}	**2m**	60

[a] Reaction conditions: **1** (0.2 mmol), I_2 (0.6 mmol), anhydrous MeOH (0.1 M), room temperature, 2–5 hours. [b] Isolated yield.

Similarly, the 4-pentyl substituted 4-hydroxy-but-2-yn-1-ones **1g–k** having various substituted phenyl groups, naphthyl group, and alkyl group at R^2 underwent the cyclization smoothly to give the products in high yields (entries 6–10). Substrates **1l** and **1m** having a primary propargyl alcohol moiety were also compatible with the standard reaction conditions, affording the trisubstituted furans **2l** and **2m** in good yields (entries 11 and 12).

We further tested this cyclization with an IBr electrophile instead of iodine. Fortunately, in the presence of two equivalents of IBr, substrates **1b**, **1g**, and **1n** underwent the electrophilic cyclization smoothly to afford the corresponding 3-bromo-4-iodofurans in good yields (eqn (4)). The structure of **2b′** was unambiguously confirmed by X-ray crystal-structure analysis.[7]

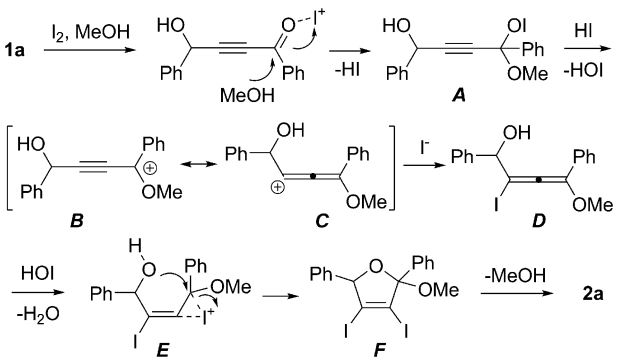


1b R^1 = Ph, R^2 = 4-MeO-C_6H_4 **2b'** 75%
1g R^1 = n-C_5H_{11}, R^2 = Ph **2g'** 57%
1n R^1 = Ph, R^2 = 2-thienyl **2n'** 48%

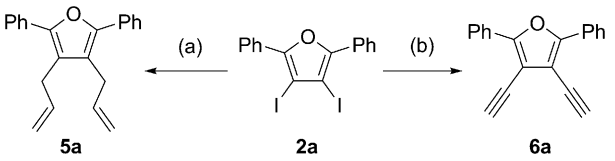
(4)

A plausible mechanism for the present cyclization is shown in Scheme 1. Presumably, initial activation of butynone **1a** with a Lewis acidic iodine[8] in the presence of MeOH leads to the ketal intermediate **A**.[9] Subsequent dehypoiodination gave propargylic carbocation **B** or allene cation **C**[10] along with an unstable hypoiodous acid (HOI) and an iodine anion. Attack of the iodine anion onto the γ-position of **B** or the cation **C** affords iodoallene **D** which will react with hypoiodous acid to form an iodonium intermediate **E**.[11] Subsequent intramolecular nucleophilic addition of an oxygen atom to the activated allene **E** followed by elimination of MeOH produces **2a**.

We carried out the following control experiments to confirm the proposed mechanism. From the reaction of *E*-configured diiodo hydroxyl enone **3a** with I_2 under the standard conditions in CH_2Cl_2, **2a** was obtained in 40% yield together with the recovered **3a** in 50% yield (eqn (5)). **2a** must be formed through a mechanism similar to the previously reported one by Obrecht[2a] and Müller *et al.*,[2g,h] in which the interconversion of the (*E*)- and (*Z*)-isomers followed by intramolecular cyclocondensation takes place. On the other hand, the reaction of **3a** in MeOH did not produce the corresponding product **2a** at all. Moreover, when the substrate **1o**, without a proton at the propargyl alcoholic carbon, was treated with I_2 under the standard conditions, the methoxy incorporated dihydrofuran **4o** was obtained in 83% yield (eqn (6)). These results indicate that the present cyclization

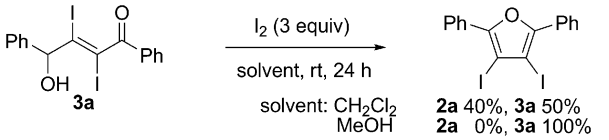


Scheme 1 Proposed reaction mechanism.

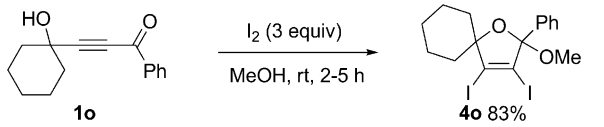


Scheme 2 (a) $Pd(PPh_3)_4$ (20 mol%), LiCl, DMF, allyltributylstannane, 100 °C, 83%; (b) (i) $Pd(PPh_3)_2Cl_2$ (5 mol%), CuI (10 mol%), DIPA, THF, 60 °C, ethynyltrimethylsilane. (ii) K_2CO_3, MeOH/THF, rt, 70% for 2 steps.

must proceed through the formation of the ketal intermediate **A** in the presence of MeOH.



(5)



(6)

As shown in Scheme 2, diiodofuran **2a** was readily converted to the tetrasubstituted furans using various Pd-catalyzed processes. For example, the double Stille couplings of **2a** with allyltributylstannane gave the bisallylated product **5a** in 83% yield. Similarly, the double Sonogashira couplings of **2a** with trimethylsilyl acetylene afforded the corresponding product **6a** in 70% yield after deprotection of TMS-groups.

In conclusion, we have developed a facile, efficient, and general method for the synthesis of dihalofurans through electrophilic iodocyclization. This methodology accommodates a wide range of functional groups and affords various highly substituted 3,4-diiodo- and 3-bromo-4-iodo-furans efficiently under mild reaction conditions. The reaction proceeds through ketals generated *in situ* in MeOH. The resulting diiodo compounds can be readily transferred to the multi-π-system substituted furans by Pd-catalyzed transformations. Application of the present method to the synthesis of useful optoelectronic materials is in progress.

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Notes and references

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