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Diversified assembly of perfluoroalkyl-substituted furans and 2,5-dihydrofuran-2-ols

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ABSTRACT

We have developed a facile and effective synthesis of 3-iodofurans from 3-monosubstituted 1,2-allenyl perfluoroalkyl ketones or 2-hydroxy-4-iodo-2,5-dihydrofurans from 3,3-disubstituted 1,2-allenyl perfluoroalkyl ketones. The perfluoroalkyl substituent and the amount of water in the solvent are important for the success of this electrophilic cyclization.

As one of the most important classes of heterocyclic compounds, furans are not only significant components in many natural products but also useful building blocks in organic synthesis. On the other hand, many attentions have been paid to the electrophilic reaction of allenes,[1,2] especially the electrophilic cyclization of allenoates,[3] allenoic acids[4], and allenols[5] with electrophiles such as I_2, Br_2, PhSeCl, we envisioned that electrophiles such as I_2, NIS, and NBS would react with 1,2-allenyl ketones **1** to form intermediates **M1**. Then if R^2 is equal to hydrogen, the intermediates **M1** would form furans **2** through aromatization by releasing H^+; if R^2 is not equal to hydrogen, H_2O would attack the C=O double bond to form 2-hydroxy-2,5-dihydrofurans **3**. This may open a new access to synthesis of polysubstituted furans or 2,5-dihydrofuran-2-ols (Scheme 1). However, we had very limited success on such electrophilic cyclization of 1,2-allenyl ketones. The reason is obvious: 1,2-allenyl ketones are too electron-deficient. Recently, we have developed a useful synthesis of allenyl perfluoroalkyl ketones.[6] We observed that the R_f-substituted carbonyl group is not very reactive toward nucleophilic reagents, such as Grignard reagent, indicating a nature of less electron-withdrawing of the R_fCO group, which promoted us to study the corresponding electrophilic cyclization reaction. As we know fluoroalkyl-substituted furans are important unit in some biologically active compounds showing anticancer, antibacterial, and antiparasite activities (Fig. 1).[7,8] Herein, we wish to report our recent studies on the electrophilic cyclization of perfluoroalkyl allenyl ketones.

We initiated this study with the electrophilic cyclization of 1-phenylbuta-1,2-dien-3-yl *n*-perfluorobutyl ketone **1a** with I_2. Interestingly, when the reaction of **1a** was carried out at room temperature in anhydrous CH_3CN,[9] the expected *n*-perfluorobutyl-substituted iodofuran **2a** was formed in 93% NMR yield with 2% recovery of **1a** in 36 h (entry 1, Table 1). At a higher temperature such as 40 °C or 60 °C, the reaction time could be shortened without decreasing the yield, but an unidentified byproduct was formed which could not be separated from the main product **2a** (entries 2–3, Table 1). According to the previous experiences, we know that water may play a critical role in such reaction.[10] We used CH_3CN with the addition of 1.0 equiv of water as the reaction media to test the reaction. Fortunately, the **2a** was formed in 99% NMR yield within 36 h at room temperature (entry 4, Table 1). However, adding more equiv of water to CH_3CN (5.0 equiv) hampered the reaction and gave the product **2a** in low yields (entry 5, Table 1). Other solvents such as DMSO, DMA, THF, Et_2O were also examined without better results (entries 6–9, Table 1).

Having established an optimal protocol, we next investigated the generality and the scope of the reactions with the results being summarized in Table 2. Excellent yields were given when R^1 is a phenyl group (entries 1–3, Table 2) while moderate to good yields were given when R^1 is an alkyl group (entries 4–7, Table 2). When R^3 was propyl group, a higher temperature (60 °C) or I_2 (4.0 equiv) was necessary to consume the starting allenone completely (compare entry 3 with entry 1, entry 7 with entry 5, Table 2). The reactivity of *n*-perfluorohexyl ketone **1f** with a longer perfluoroalkyl chain is low, and thus 4.0 equiv of I_2 were needed to complete the reaction (compare entry 6 with entry 4, Table 2). When 1,3,3-trisubstituted ketones **1h–j** were applied to the reactions, 4-iodo-2,5-dihydrofuran-2-ols **3h–j** were formed as expected (entries 8–10, Table 2). When the reaction of **1j** was conducted at aqueous CH_3CN (CH_3CN/H_2O = 20/1), the yield of the product **3j** was improved to 88% yield (entry 11, Table 2).

In conclusion, we have developed a facile and effective synthesis of 3-iodofurans from 3-monosubstituted 1,2-allenyl perfluoroalkyl ketones or 2-hydroxy-4-iodo-2,5-dihydrofurans from 3,3-disubstituted 1,2-allenyl perfluoroalkyl ketones. The presence of the perfluoroalkyl substituent is important for the success of the electrophilic cyclization. Since the normal 1,2-allenyl ketones did not work on this type of electrophilic iodocyclization, this protocol may be informative for further study in this area. Further studies in this area are being pursued in our laboratory.

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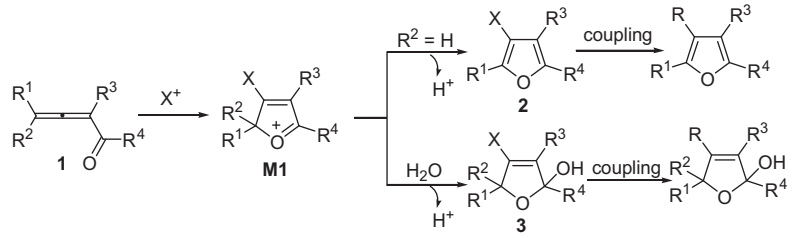


Scheme 1. Electrophilic cyclization of 1,2-allenyl ketones.

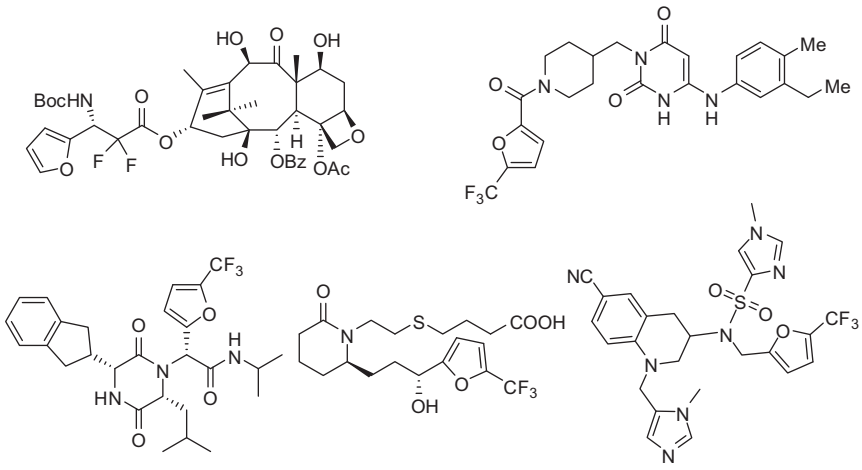
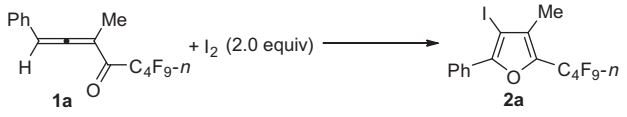


Figure 1. Biologically active compounds with fluorine-containing furan unit.

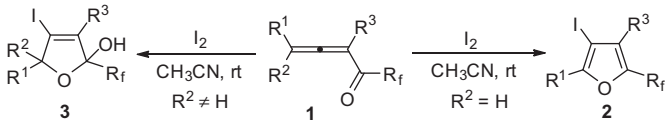
Table 1
Optimization of reaction conditions[a]



Entry	Solvent	H_2O (equiv)	Temp. (°C)	Time (h)	Yield[b] of **2a**	Recovery of **1a**
1	MeCN	0	rt	36	93	2
2[c]	MeCN	0	40	22	95	0
3[c]	MeCN	0	60	11	93	0
4	**MeCN**	**1**	**rt**	**36**	**99** (**93**)	**0**
5	MeCN	5	rt	36	81	0
6	DMSO	1	rt	32	5	1
7	DMA	1	rt	32	45	0
8	THF	1	rt	40	17	61
9	Et_2O	1	rt	40	58	18

[a] The reaction was conducted by treating **1a** with 2.0 equiv of I_2.
[b] Yields were determined by ^1H NMR analysis with mesitylene as the internal standard.
[c] An unidentified byproduct was formed which could not be separated from the main product **2a**.

Table 2
Reactions of 1,2-allenyl perfluoroalkyl ketones with I_2[a]



Entry	R^1	R^2	R^3	R_f	Time (h)	Yield (%)
1	Ph	H	Me	n-C_4F_9 (**1a**)	36	93 (**2a**)
2	Ph	H	Me	n-C_6F_{13} (**1b**)	36	91 (**2b**)
3[b]	Ph	H	n-C_3H_7	n-C_4F_9 (**1c**)	16	91 (**2c**)
4	n-Bu	H	Me	n-C_4F_9 (**1d**)	36	60 (**2d**)
5	n-C_7H_{15}	H	Me	n-C_4F_9 (**1e**)	36	60 (**2e**)
6[c]	n-Bu	H	Me	n-C_6F_{13} (**1f**)	24	85 (**2f**)
7[c]	n-C_7H_{15}	H	n-C_3H_7	n-C_4F_9 (**1g**)	36	70 (**2g**)
8	$-(CH_2)_5-$		Me	n-C_4F_9 (**1h**)	37	75 (**3h**)
9	Me	Me	Ph	n-C_4F_9 (**1i**)	35	93 (**3i**)
10[d]	Ph	Ph	n-C_3H_7	n-C_4F_9 (**1j**)	35	54 (**3j**)
11[e]	Ph	Ph	n-C_3H_7	n-C_4F_9 (**1j**)	16	88 (**3j**)

[a] The reaction was conducted by treating **1** with I_2 (2.0 equiv) and H_2O (1.0 equiv) in MeCN at rt.
[b] The reaction was conducted at 60 °C, and the purity of **2c** was 98%.
[c] Using 4.0 equiv of I_2.
[d] The starting material **1j** was recovered 29%.
[e] MeCN/H_2O = 20/1.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.085.

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