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Iodocyclization of Ethoxyethyl Ethers to Alkynes: A Broadly Applicable Synthesis of 3-Iodobenzo[*b*]furans

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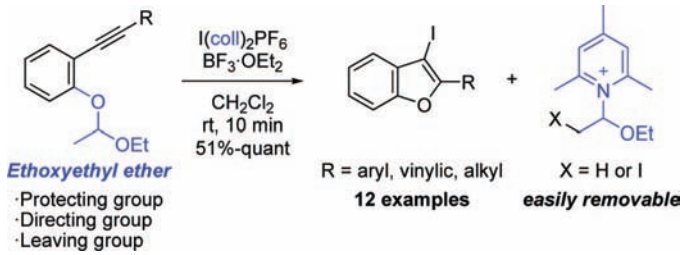
ABSTRACT



A wide variety of 3-iodobenzo[*b*]furans were readily prepared by iodocyclization of 2-alkynyl-1-(1-ethoxyethoxy)benzenes with the $I(coll)_2PF_6-BF_3{\cdot}OEt_2$ combination. Aryl-, vinylic-, and alkyl-substituted alkynes undergo iodocyclization in good to excellent yields. The mechanism of the reaction is also discussed.

The benzo[*b*]furans are attractive synthetic target molecules due to the wide spectrum of their biological activities in natural and unnatural compounds.[1] Numerous efficient methods for the synthesis of the benzo[*b*]furans have been developed.[2,3] Among them, iodocyclization of 2-alkynylphenol derivatives is a powerful method for the construction of 3-iodobenzo[*b*]furans due to the potential for further functionalization at the C−I bond by metal-catalyzed cross-coupling.[3]

Arcadi et al. reported the synthesis of 3-iodobenzo[*b*]furans by iodocyclization of 2-alkynylphenols (eq 1).[3a] However, their method requires a series of protecting and deprotecting steps for the preparation of 2-alkynylphenols, which are also relatively unstable. Larock and Colobert et al. reported the iodocyclization of 2-alkynylanisoles, which are stable and more easily prepared in fewer steps than in Arcadi's procedure (eq 2).[3b,c] Although the 2-aryl-3-iodobenzo[*b*]-furans were successfully synthesized by these methodologies, the application for 2-*alkyl* derivatives has been limited due

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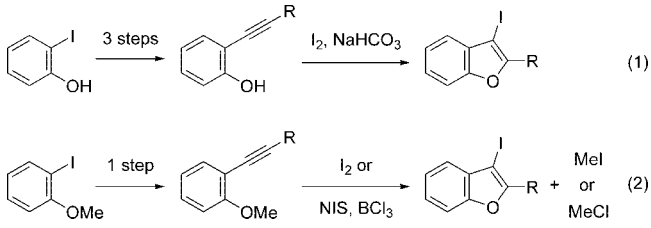
to 1,2-addition of I_2 to alkynes. In addition, carcinogenic and volatile halomethanes (MeI or MeCl) can be formed in the reactions by these earlier methods. Therefore, we sought a safer, more general procedure for the efficient synthesis of both 2-aryl- and 2-alkyl-3-iodobenzo[*b*]furans.



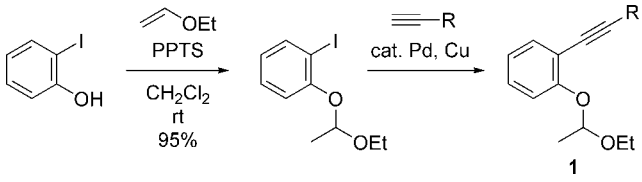
(1)

(2)

Herein, we report an iodocyclization of ethoxyethyl ethers to alkynes for the synthesis of 3-iodobenzo[*b*]furans. The advantages of our method are as follows: (1) ethoxyethyl ether serves not only as the protecting group but also as a directing group for the preparation of precursors for iodocyclization; (2) the synthesis requires a reasonable number of steps from starting material to 3-iodobenzo[*b*]furans; (3) the title compounds are afforded not only in short reaction time (10 min) but also in high yields without the generation of hazardous halomethanes; and (4) 2-*alkyl*-3-iodobenzo[*b*]-furans can also be obtained in good yields.

2-Alkynyl-1-(1-ethoxyethoxy)benzenes **1**, the precursors for iodocyclization, were prepared by the conversion of 2-iodophenol to the ethoxyethyl ether[4] followed by Sonogashira coupling with terminal alkynes (Scheme 1).[5] Notably,

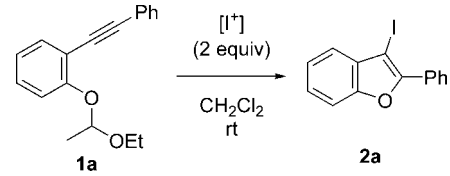
Scheme 1. Preparation of the Precursors in Iodocyclizaton



the ethoxyethyl ether could be used as a directing group.[6] Thus, α-lithiation of 1-(1-ethoxyethoxy)naphthalene and iodination with I_2 followed by Sonogashira coupling with phenylacetylene afforded a naphthol derivative **1h** (see the Supporting Information).

We first examined the reaction of **1a** toward the iodinating reagents (Table 1). Each reaction was performed with 2 equiv of the iodinating reagents in a 0.1 M CH_2Cl_2 solution of **1a** at room temperature. Whereas I_2 was poor for the iodocyclization, ICl afforded **2a** in good yield (entries 1−3). However, in each case, 1,2-addition of I_2 or ICl across the alkyne occurred as a side reaction. We considered that a

Table 1. Optimization of Iodocyclization of **1a**



1a **2a**

entry	$[I^+]$ source	additive (equiv)	time	**2a** (yield, %)
1	I_2	none	2 h	3
2	I_2	$NaHCO_3$ (2)	2 h	0
3	ICl	none	10 min	84
4	NIS	none	23 h	43
5	IPy_2BF_4	none	20 h	96
6	$I(coll)_2PF_6$	none	24 h	92
7	$I(coll)_2PF_6$	$BF_3{\cdot}OEt_2$ (4)	10 min	98
8	$I(coll)_2PF_6$	$BF_3{\cdot}OEt_2$ (2)	10 min	quant
9[a]	$I(coll)_2PF_6$	$BF_3{\cdot}OEt_2$ (1)	24 h	51
10	NIS	$BF_3{\cdot}OEt_2$ (2)	10 min	40

[a] 1 equiv of $I(coll)_2PF_6$ was added.

decrease of the nucleophilicity of the counteranion would suppress the addition reaction. Therefore, *N*-iodosuccinimide (NIS), bis(pyridine) iodonium tetrafluoroborate (IPy_2BF_4), and bis(2,4,6-collidine)iodonium hexafluorophosphate ($I(coll)_2PF_6$) were examined as iodinating reagents, and IPy_2BF_4 and $I(coll)_2PF_6$ provided superior yields of **2a** (entries 4−6). IPy_2BF_4 was more expensive than $I(coll)_2PF_6$, so the latter reagent was used for further optimization.[7] We found that $BF_3{\cdot}OEt_2$ as an additive enhanced the reaction rate to afford **2a** in quantitative yield within only 10 min (entries 7 and 8).[8] A diminishment of reagent equivalents or the combination of NIS−$BF_3{\cdot}OEt_2$ in place of $I(coll)_2PF_6$−$BF_3{\cdot}OEt_2$ decreased the yields of **2a** (entries 9 and 10). To the our best knowledge, this is the first report of an iodocyclization with an ethoxyethyl ether serving as an oxygen nucleophile toward alkynes.[9]

Once the optimized conditions were established as in entry 8 (Table 1), various substrates were next examined (Table 2). Other acetal-type protecting groups, such as MOM (methoxymethyl) and THP (tetrahydropyranyl) ethers, were effective, but the yields were less than with the ethoxyethyl ether derivative (entries 1 and 2). When the substituent on the alkyne was aryl and vinylic, with sp^2 carbon centers, 2-aryl- and 2-vinylic-3-iodobenzo[*b*]furans were obtained in high to excellent yields (entries 3−5). The presence of substituents on the aromatic core did not influence the iodocyclizations (entries 6 and 7). It is noteworthy that *alkyl*-

(4) Fukuzawa, A.; Sato, H.; Masamune, T. *Tetrahedron Lett.* **1987**, *28*, 4303–4306.

(5) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470.

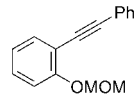
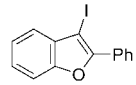
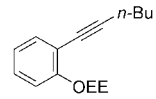
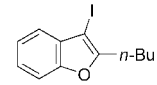
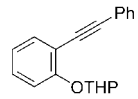
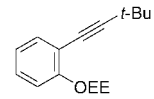
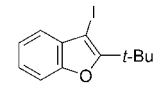
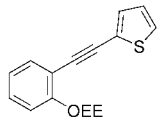
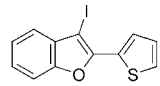
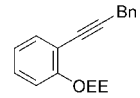
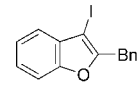
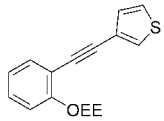
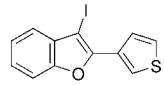
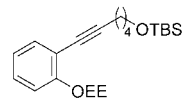
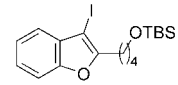
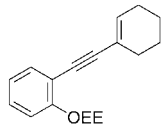
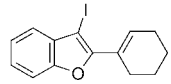
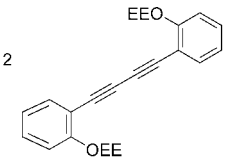
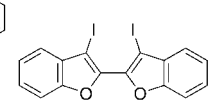
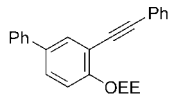
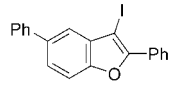
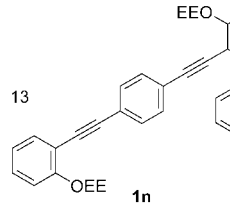
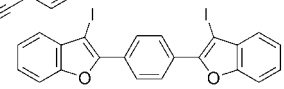
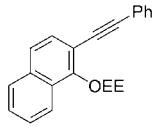
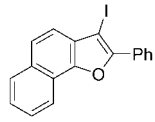
(6) MOM ether as a directing group: Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, *22*, 3923–3924.

(7) The price per gram is 10300 yen for IPy_2BF_4 and 2560 yen for $I(coll)_2PF_6$; source Aldrich catalogue 2007−2008.

(8) IPy_2BF_4 can be activated by Lewis acid; see: Barluenga, J.; Campos, P. J.; González, J. M.; Suárez, J. L. *J. Org. Chem.* **1991**, *56*, 2234–2237. (b) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406–2409. (c) Barluenga, J.; Trincado, M.; Marco-Arias, M.; Ballesteros, A.; Rubio, E.; González, J. M. *Chem. Commun.* **2005**, 2008–2010.

(9) For $PtCl_2$-catalyzed carboalkoxylation of *o*-alkynylphenyl acetals, see: Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022–15023.

Table 2. Synthesis of 3-Iodobenzo[*b*]furans **2a**−**n** by Iodocyclization[a]

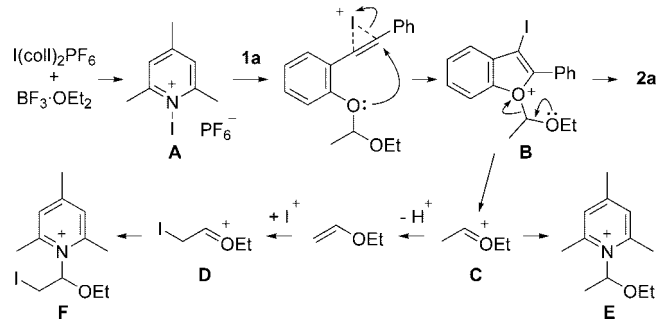
entry	substrate	product (yield%)	entry	substrate	product (yield%)
1	 **1b**	 **2a** (76)	8	 **1i**	 **2i** (70)
2	 **1c**	**2a** (83)	9	 **1j**	 **2j** (88)
3	 **1d**	 **2d** (97)	10	 **1k**	 **2k** (53)
4	 **1e**	 **2e** (quant)	11	 **1l**	 **2l** (56)
5	 **1f**	 **2f** (74)	12	 **1m**	 **2m** (51)[b]
6	 **1g**	 **2g** (95)	13	 **1n**	 **2n** (68)[b]
7	 **1h**	 **2h** (95)			

[a] EE: ethoxyethyl, conditions: $I(coll)_2PF_6$ (2 equiv), $BF_3{\cdot}OEt_2$ (2 equiv), CH_2Cl_2, rt, 10 min. [b] Conditions: $I(coll)_2PF_6$ (4 equiv), $BF_3{\cdot}OEt_2$ (4 equiv), CH_2Cl_2, rt, 10 min.

(sp^3 carbon center-)substituted alkynes **1i**−**l** were also applicable in these reaction conditions (entries 8−11). To our best knowledge, only one example of the synthesis of a 2-*alkyl*-3-iodobenzo[*b*]furan has been reported.[3a] Thus, our novel reaction conditions may afford a more widely adaptable synthetic route to 2-*alkyl*-3-iodobenzo[*b*]furans. Of the alkyl substituents, not only primary but also tertiary alkyl groups were allowed. Our method was also acceptable in a gram scale procedure (entry 9, see the Supporting Information). Even the substrate containing an oxygen function at the terminal alkyne **1l** afforded **2l** in moderate yield. Furthermore, double-iodocyclization was achieved by using 4 equiv of $I(coll)_2PF_6$ and $BF_3{\cdot}OEt_2$ (entries 12 and 13).

Based on the outcomes of these reactions, we developed a plausible reaction mechanism for the iodocyclization (Scheme 2). From the reaction of $I(coll)_2PF_6$ and $BF_3{\cdot}OEt_2$, active iodonium species **A** is generated.[8] The *anti* attack of the electrophile and the oxygen of the ethoxyethyl ether on the alkyne gives intermediate **B**, which undergoes the loss

Scheme 2. Plausible Reaction Mechanism

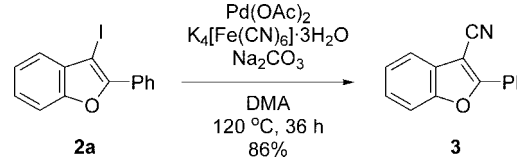


of the ethoxyethyl group to afford the 3-iodobenzo[*b*]furans. The oxonium ions **C** and **D** are trapped by 2,4,6-collidine to afford collidinium salts **E** and **F**.[10] Intermediates **A**−**F** were confirmed by SIMS study of the reaction mixture of **1a** (see the Supporting Information). More- over, instead of generating hazardous halomethanes,[3b,c] our method produced highly polar compounds **E** and **F** together, which are stable and easily removable by column chromatography on silica gel. Thus, our synthetic method for 3-iodobenzo[*b*]furans was totally safe and applicable to various substrates.

The 3-iodobenzo[*b*]furans can be further functionalized by palladium-catalyzed coupling reactions at the C−I bond. Arcadi et al. have reported the Sonogashira coupling reaction, Heck reaction, and methoxycarbonylation of **2a**.[3a] We also elaborated a cyanation of **2a** by $Pd(OAc)_2$ and $K_4[Fe(CN)_6]$, a nontoxic cyanide source, to yield 3-cyanobenzo[*b*]furan **3** in 86% yield (Scheme 3).[11] The nitrile group could then utilized for further transformations.[12]

In summary, we have constructed 3-iodobenzo[*b*]furans through the iodocyclization of ethoxyethyl ether to alkynes. The substituents on alkyne, sp-, sp^2-, and sp^3-carbon center were available. These iodo derivatives have the possibility for further functionalization by metal-catalyzed cross-coupling. This research provides a new synthetic method for natural and unnatural compounds containing the benzofuran skeleton. Further investigations into the scope and limitations of the iodocyclization are ongoing.

Scheme 3. Cyanation of **2a**



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Supporting Information Available: Experimental details and characterization data of compounds **1a**−**n**, **2a**−**n**, and **3**. Copies of ^1H and ^{13}C NMR spectra of all new compounds and SIMS spectra of the reaction mixture. This material is available free of charge via the Internet at http://pubs.acs.org.

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