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Facile access to 2,5-disubstituted-4-chloromethyl-3-iodofuran derivatives via ICl-mediated cyclization of 1-alkyl-2-alkynylallylic alcohols

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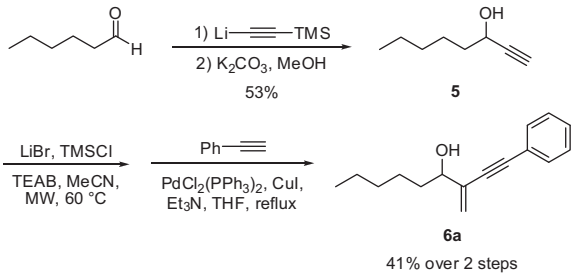
ABSTRACT

Substituted furans are conveniently synthesized from acyclic secondary 1-alkyl-2-alkynylallylic alcohol precursors via an ICl-promoted cyclization reaction. The furans generated by this method incorporate both iodine and chlorine atoms which may be useful for further elaborations via many known methods. The methodology is suitable for generating a wide array of furan products which can serve as useful building blocks for the synthesis of various biologically active molecules.

Furan is a widespread heterocyclic motif found in nature.[1] It is present in compounds used as major constituents in fragrance and flavor components, agrochemical substances, as well as in pharmaceutical ingredients.[2] In addition to serving as active entities in many commercial products, furans also serve as versatile and valuable building blocks which can be elaborated to more complex cyclic and acyclic structures of theoretical and biological interest.[3]

Numerous methods have been devised to construct furan derivatives. These include intramolecular cyclization of an oxygen-functional group onto a tethered unsaturated bond of an appropriate length using bases,[4] transition metal compounds,[5] and electrophilic halogens; particularly molecular iodine (I_2), *N*-iodosuccinimide (NIS), and *N*-bromosuccinimide (NBS).[6] The products obtained using the latter methods usually contain a halogen atom directly attached to the five-membered nucleus,[7] which may be further utilized. Our research emphasizes particularly the utilization of an enyne tethered to an oxygen-functional group in such cyclizations, which would provide a simple template for the synthesis of functionalized furan derivatives. A number of publications have utilized acyclic oxygenated enyne precursors in such reactions to produce efficiently polysubstituted furan derivatives. The methodology devised for such cyclizations include the base-promoted cyclization of enynyl alcohols of types **1** and **2**,[8] gold-catalyzed cyclization of enynyl alcohols[9] of types **1**[10a] and **2**,[10b,c] and gold-catalyzed and I_2-promoted cascade cyclization–nucleophilic substitution of enynyl ketones of types **3** and **4**.[11] Herein, we wish to report our protocol for the facile synthesis of 2,5-disubstituted-4-chloromethyl-3-iodofuran derivatives from substituted enynyl alcohols of type **1**.

We began our investigation by preparing enynyl alcohol **6a** for the optimization study. Thus hexanal was treated with lithium TMS-acetylide in THF, followed by a standard desilylation protocol to provide propargylic alcohol **5** in 53% yield. Sequential hydrobromination[12] of alcohol **5** and Sonogashira cross-coupling[13] of the resulting vinylic bromide with phenyl acetylene then furnished the desired alcohol **6a** in 41% yield over two steps (Scheme 1).



Scheme 1. Preparation of enyne **6a** for the optimization study.

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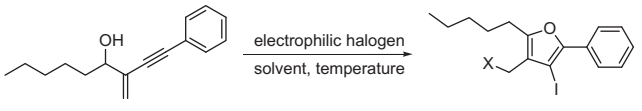
Table 1
Screening for the optimal cyclization conditions of **6a**



6a **7a**; X = Cl **7a-I**; X = I

Entry	Solvent	Reagent (equiv)	Yield[a] (%)
1	Acetone	I_2 (2.2)	NR
2	Acetone	I_2 (4.0)	NR
3	Acetone	I_2 (2.2)	NR[b]
4	THF	I_2 (2.2)	NR[b]
5	Acetone	ICl (2.2)	29
6	MeCN	ICl (2.2)	33
7	$MeNO_2$	ICl (2.2)	67
8	$MeNO_2$	ICl (2.2)	59[c]
9	THF	ICl (2.2)	47
10	Hexane	ICl (2.2)	36
11	Toluene	ICl (2.2)	18[d]
12	CH_2Cl_2	ICl (2.2)	26
13	$CHCl_3$	ICl (2.2)	46
14	MeOH	ICl (2.2)	Dec

[a] Isolated yield.
[b] $NaHCO_3$ was employed as an additive.
[c] Reaction was conducted at 0 °C.
[d] Reaction was stirred overnight at rt to reach completion.

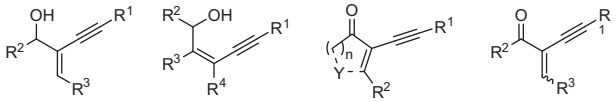


Figure 1. Oxygenated conjugated enynes used in furan synthesis.

We next attempted the cyclization of alcohol **6a**, the results of which are summarized in Table 1. Initially, we found that excess I_2 was inactive toward the cyclization of this alcohol even in the presence of $NaHCO_3$ (entries 1–4); no furan **7a–I** was obtained. This was in a stark contrast to Larock's ketone substrates (**3** and **4**; Fig. 1) which readily underwent cyclization to give the desired furan products.[11] When 2.2 equiv of ICl was employed to initiate the cyclization in acetone, the reaction proceeded to completion very rapidly and we were able to isolate a product. Initially, furans **7a–I** was anticipated from the reaction. However, the product isolated was found to be furan **7a**[14] which was obtained in 29% yield (entry 5). Observing this positive outcome with ICl, we proceeded to investigate the effect of different solvents on this cyclization reaction (entries 6–14).

In acetonitrile, enyne **6a** was converted cleanly to give furan **7a**, albeit in only 33% yield (entry 6). In nitromethane, furan **7a** was obtained in high yield (67%)[15] while the yield was lower (59%) when the reaction was conducted at 0 °C (entries 7 and 8).[16] We suspected that at lower temperature, the cyclization proceeded less readily which allowed other side-reactions to occur. We also attempted the reaction in tetrahydrofuran, hexane, toluene, dichloromethane, and chloroform (entries 9–13) and found that the yield could not be improved greater than 47%. It should be noted that all of these reactions proceeded to completion very rapidly, except in toluene when the reaction required overnight stirring at room temperature to achieve full conversion. Thus using the optimal conditions, enynyl alcohol **6a** was cleanly and rapidly (within 5 min) converted into iodofuran **7a** in 67% yield when treated with 2.2 equiv of ICl in nitromethane at room temperature.[17]

After finding the optimal conditions for the cyclization of **6a**, we next studied the scope of the reaction by applying these conditions to other alkynylallylic alcohols (**6b–6k**)[18] and the results are summarized in Table 2.[19] For the secondary enynyl alcohols substituted with an *n*-pentyl group (entries 1–4), the cyclization of the hydroxyl group onto the triple bond substituted with aryl substituents occurred readily to give the corresponding furan products in 45–67% yields. Aryl rings containing either electron-donating (**6b–6c**; entries 2 and 3) or electron-withdrawing (**6d**; entry 4) groups gave lower yields of the corresponding furans compared to compound **6a**. However, among the substituted aromatic systems, substrates containing electron-donating groups gave better yields of products than those containing an electron-withdrawing group (compare entries 2 and 3 and entry 4). It is noteworthy to mention that we did not observe over-halogenation in any of the products containing the electron-rich phenyl ring, for example, **7c** (entry 3).

For the phenethyl substituted secondary enynyl alcohols (entries 5–9), the reactions also proceeded readily to give the corresponding furan products in 32–81% yields. Among these

Table 2
Scope of the ICl-promoted cyclization of alkynylallylic alcohols **6**[a]

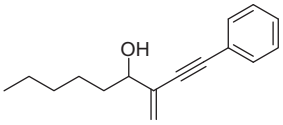
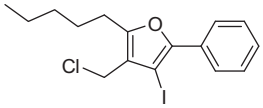
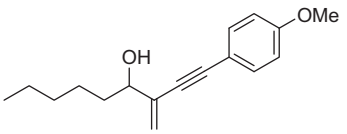
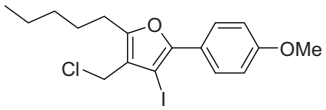
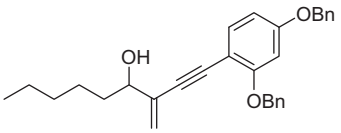
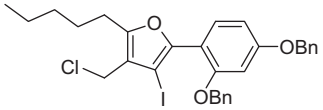
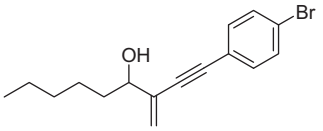
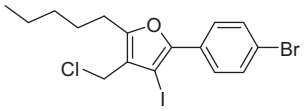
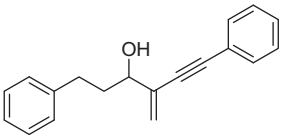
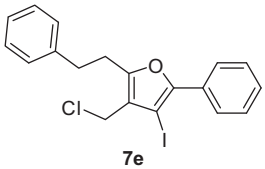
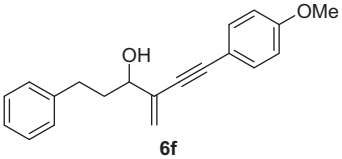
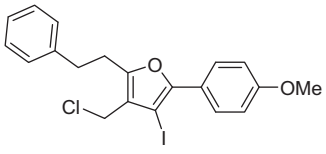
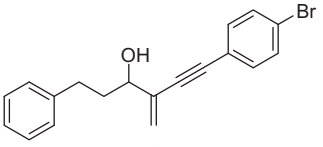
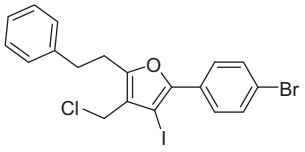
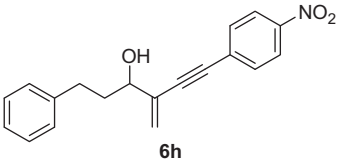
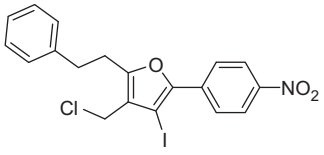
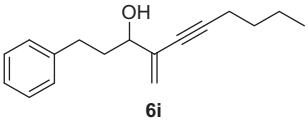
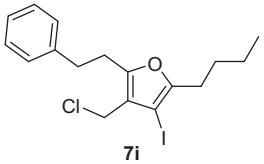
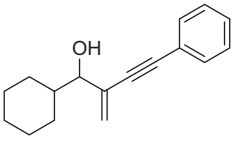
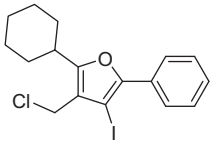
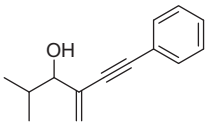
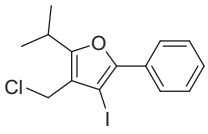
Entry	Substrate	Product	Yield[b] (%)
1	 **6a**	 **7a**	67
2	 **6b**	 **7b**	57
3	 **6c**	 **7c**	62

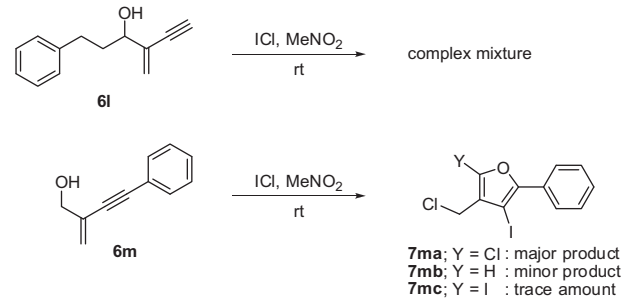
Table 2 (*continued*)

Entry	Substrate	Product	Yield[b] (%)
4	 **6d**	 **7d**	45
5	 **6e**	 **7e**	81
6	 **6f**	 **7f**	53
7	 **6g**	 **7g**	46
8	 **6h**	 **7h**	45
9	 **6i**	 **7i**	32
10	 **6j**	 **7j**	68
11	 **6k**	 **7k**	71

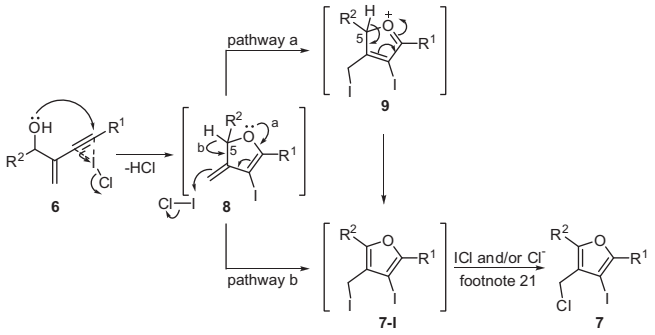
[a] Alcohol **6** (1.0 equiv) in $MeNO_2$ (0.05 M) was treated with ICl (2.2 equiv) as a solution in $MeNO_2$.
[b] Isolated yield.

substrates, the trend in yields was consistent with the *n*-pentyl series (vide supra). For the non-substituted phenyl substituent on the triple bond, the cyclized product was obtained in high yield (entry 5). However, when this phenyl ring was substituted with either electron-donating (**6f**) or electron-withdrawing groups (**6g**–**6h**), the yields were lower (45–53%; entries 6–8). Among these entries, the substrate containing an electron-donating group provided a slightly better yield of the corresponding product (compare entry 6 and entries 7 and 8). When the substrate containing an *n*-butyl-substituted alkyne (**6i**) was subjected to the optimal cyclization conditions, furan **7i** was obtained in only 32% yield. In other secondary enynyl alcohols substituted with cyclohexyl and *i*-propyl groups, the cyclization readily occurred to give the desired furans **7j** and **7k** in 68% and 71% yields, respectively (entries 10 and 11).

In addition to the substrates in Table 2, these cyclization conditions were applied to enynyl alcohols **6l** and **6m**. With alcohol **6l**, which contained a terminal alkyne, the reaction proceeded to give



Scheme 2. ICl-promoted cyclization of alcohols **6l** and **6m**.



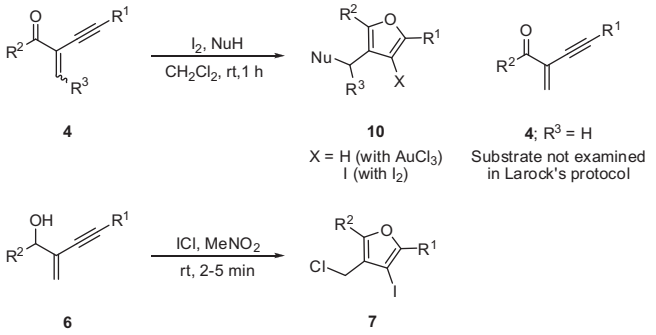
Scheme 3. Proposed reaction mechanisms.

a complex mixture as observed by both TLC and ^{1}H NMR spectroscopy. For primary enynyl alcohol **6m**, however, the reaction proceeded to give three different products in low combined yields as shown in Scheme 2. The initial furan product **7mb** underwent further chlorination to give dichlorinated furan **7ma** as the major component in this mixture. A trace amount of diiodinated furan **7mc** from iodination of **7mb** was also detected by HRMS. The direct chlorination of furan **7mb** by ICl may be possible as this reagent has been reported to be able to act as a chlorinating agent.[20]

The proposed mechanism for the cyclization is shown in Scheme 3. The reaction is believed to begin with coordination of ICl to the triple bond of the alkyne, followed by intramolecular nucleophilic addition of the hydroxyl group to give intermediate **8**. The reaction could then take place via one of two possible pathways (Scheme 3). In pathway a, a lone pair of electrons on the oxygen atom could assist in the electrophilic iodination with another molecule of ICl at the methylene carbon to give the oxonium intermediate **9** which quickly re-aromatized to the initial furan product **7-I**. In pathway b, the re-aromatization of intermediate **8**, which occurred via loss of a proton at C-5, concurrently with the electrophilic iodination with another molecule of ICl at the methylene carbon, directly furnished the furan product (**7-I**). In the presence of chloride (generated during the reaction) and/or excess ICl, furan **7-I** was rapidly converted into the desired iodofuran **7**.[21]

The current method draws similarity with the previous study by Larock and co-workers,[11] whose protocol typically employed substrates of types **3** and **4** (Fig. 1). However, no example of enynone substrates containing a 1,1-disubstituted double bond (**4**; R^3 = H) were reported. Our work complements the work of Larock's in that it has demonstrated the viability in which enynyl alcohols, instead of ketones, containing a 1,1-disubstituted double bond could participate in ICl-initiated cyclization to furnish the corresponding iodofuran products (Scheme 4).

In conclusion, we have demonstrated that ICl is an efficient electrophilic halogenating agent which induces cyclization of secondary enynyl alcohols **6**. The cyclization occurred very rapidly



Scheme 4. Comparison between Larock's and our protocols.

(within 5 min) and the enynyl alcohol substrates were completely converted into the dihalofuran products in moderate to excellent yields. The method reported herein should provide a simple and efficient access to multi-substituted furan derivatives, which might be useful as building blocks for the synthesis of complex organic compounds.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.124.

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14. Compound **7a** showed chemical shifts in the ^{13}C NMR spectrum at 38.5 ppm which belonged to the chloromethylene carbon at the C-4 position of the furan ring, and at 66.4 ppm due to the carbon bearing iodine at C-3 position of the furan ring. The identity of furan **7a** was further confirmed by HRMS which revealed the molecular formula $C_{16}H_{18}ClIO$. See Ref. 17 below and Supplementary data for more details.
15. As a general practice, the reaction was worked up immediately after full conversion of the starting material was observed by TLC.
16. In addition, we attempted the reaction in the presence of $NaHCO_3$ as an additive (2.2 equiv) and observed the reaction to proceed more slowly than without it. In light of this observation, we decided to exclude the use of a base additive in our optimal conditions.
17. *Typical experimental procedure for ICl-promoted cyclization*: Alcohol **6a** (57.0 mg, 0.25 mmol) was dissolved in $MeNO_2$ (5 mL) and added a solution of ICl (90.0 mg, 0.55 mmol) into $MeNO_2$ (1 mL). After stirring at room temperature for 5 min, the solvent was removed on a rotary evaporator and the crude product was purified by column chromatography on silica gel (10% EtOAc/hexane); the product was obtained as a colorless oil (65.0 mg, 67%). R_f (10% EtOAc/hexane) 0.48; IR (neat): ν_{max} 2956, 2929, 2859, 1610, 1485, 1261, 1089, 956, 763, 691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 7.8 Hz, 2H), 7.43 (t, J = 7.2 Hz, 2H), 7.33 (t, J = 7.5 Hz, 1H), 4.48 (s, 2H), 2.76 (t, J = 7.5 Hz, 2H), 1.76–1.67 (m, 2H), 1.37–1.36 (m, 4H), 0.91 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 150.2, 130.1, 128.3, 128.1, 126.1, 120.9, 66.4, 38.5, 31.3, 27.9, 26.6, 22.3, 13.9, LRMS (EI) m/z (rel intensity) 388 (M^+, 71), 339 (10), 331 (100), 127 (15), 77 (5). TOF-HRMS (35Cl) Calculated for $C_{16}H_{18}ClIO$ ($M^{+\cdot}$) 388.0085. Found 388.0085.
18. Substrates **6b–6k** were prepared using the same synthetic sequence as compound **6a**; see Supplementary data for detailed preparations and characterizations.
19. All the products in Table 2 were sufficiently stable at room temperature and could be handled conveniently during purification on a silica gel column, and in subsequent utilizations. However, on prolonged storage (from several hours to several weeks) we did observe decomposition, including discoloration of the compounds and conversion of these compounds into other unidentified by-products. We found that these compounds could be kept significantly longer without much change when stored frozen in benzene.
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21. For the conversion of **7-I** into **7**, chloride, generated during the reaction, could potentially displace the iodide on the methylene carbon of **7-I** in an S_N2 substitution. In addition, it has been shown that rapid dissociation of an iodine atom from an organic iodide could be induced via complexation of the iodine atom with ICl. This generates a partially positive carbon which undergoes substitution by chloride. For a detailed kinetic study of this latter process, see: Schmid, G. H.; Gordon, J. W. *J. Org. Chem.* **1983**, *48*, 4010–4013.