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Electrophilic Cyclization of 2-(1-Alkynyl)-2-alken-1-ones Using the I_2/K_3PO_4 System: An Efficient Synthesis of Highly Substituted Iodofurans

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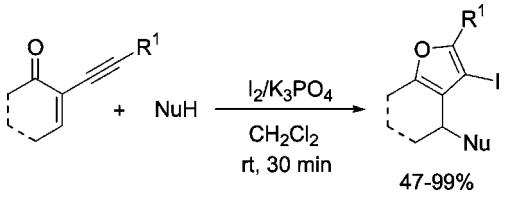
ABSTRACT



The electrophilic cyclization of 2-(1-alkynyl)-2-alken-1-ones in the presence of various alcohols or carbon-based nucleophiles offers an efficient and straightforward route to highly substituted iodofurans under extremely mild reaction conditions. The iodo derivatives are potential synthetic intermediates for amplification of molecular complexity.

The furan rings widely occur as key structural subunits in numerous natural products, which can find a variety of applications as pharmaceuticals, flavor and fragrance compounds.[1] Furthermore, highly substituted furans are of significant interest since they are useful and versatile synthetic intermediates for access to heterocyclic and acyclic compounds.[2] As a consequence, much attention has been paid to the synthesis of furan derivatives either by traditional methods[3] or by transition-metal-catalyzed reactions, including cyclization of allenyl ketones[4] and 3-alkyn-1-ones,[5] cycloisomerizations of (*Z*)-2-en-4-yn-1-ols,[6] Pd-catalyzed cyclization of (*Z*)-2-iodoalk-2-enyl ketones,[7] etc. Recently, Larock reported an interesting $AuCl_3$-catalyzed cyclization of 2-(1-alkynyl)-2-alken-1-ones leading to substituted furans[8] (eq 1).

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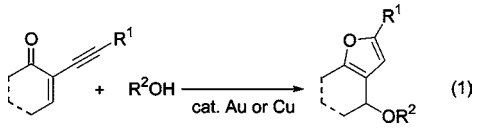
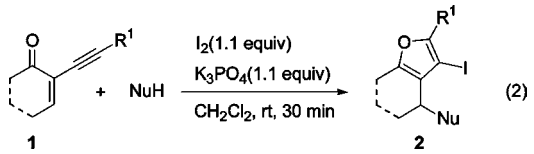
In a more recent study, the analogous cyclization reaction has been achieved using Cu(I) catalyst in DMF.[9] The metal salt employed was suggested to facilitate the reaction by a dual function as both a Lewis acid and coordination reagents with alkynes. However, in these reactions, an air-sensitive catalyst or high-temperature reaction were required.[9] In our ongoing efforts to develop new methodologies for the synthesis of heterocycles, we have succeeded in the construction of fully substituted 5-ylidene-2,5-dihydrofurans with high regio- and stereoselectivity through electrophilic cyclization of (*Z*)-enynols.[10] Halofurans are important derivatives that provide further structural elaboration by a variety of C−C, C−N, or C−S bond-forming reactions.[11]



(1)

In this paper, we report the cyclization of 2-(1-alkynyl)-2-alken-1-ones[12] by a more convenient and efficient approach involving electrophilic cyclization using a wide range of nucleophiles for the synthesis of 3-iodofuran derivatives. This procedure generally produces good to excellent yields of iodofurans in a short reaction time.

Electrophile-promoted cycloaddition of unsaturated compounds has proven to be an elegant synthetic route to the wide variety of halogenated heterocyclic compounds.[13] However, most of the recent reports focused on arylalkynes bearing ortho-related heteroatomic nucleophiles,[14] whereas only limited reports have been presented in the literature by employing other type of alkynes.[10,12,15] Here, we found that alkyne **1** readily undergoes electrophilic cyclization in the presence of a wide range of nucleophiles under mild reaction conditions (eq 2). We began our investigation with **1a** bearing a phenyl group at the end of an alkyne moiety. The reaction of **1a** in CH_2Cl_2 with methanol, iodine, and carbonate bases, such as $NaHCO_3$ (15 h, 51%) or Na_2CO_3 (3h, 88%), afforded iodinated furan **2a** in reasonable yields at room temperature. Interestingly, when K_3PO_4 was employed as a base, the desired product was isolated in 94% yield within 30 min.



(2)

The use of organic base of Et_3N resulted in the formation of **2a** in low (18%) yield. Thus, we chose the following reaction conditions for furan formation: 1.5 equiv of methanol, 1.1 equiv of I_2, and 1.1 equiv of K_3PO_4 in CH_2Cl_2 stirred at room temperature for an appropriate time. The results are summarized in Table 1. In most cases, the ring-closure products of **2a**−**2m** were obtained in good to high yields within 30 min. We first investigated the scope of nucleophiles. It was found that, in addition to methanol, a variety of alcohols could be used as effective nucleophile for this reaction. Treatment of **2a** with phenol resulted in the formation of **2b** with a phenoxy group in 80% yield. The reaction of **1a** with propargylic alcohol or allylic alcohol afforded **2c** and **2d** in 99 and 88% yield, respectively. Bulky alcohols, such as L-borneol reacted, with **1a** smoothly to give **2e** in 91% yield. Not only alcohols but also carbon nucleophiles of silyl enol ether (Table 1, entry 8) or an electron-rich aromatic compound, like *N*,*N*-dimethylaniline (Table 1, entry 9), can be used, furnishing iodocyclization products **2h** and **2i** with a newly formed carbon−carbon bond in 47 and 60% yield, respectively. The present I_2/K_3PO_4-based methodology worked well with substrates bearing an aromatic ring as well as a vinylic group at the end of alkyne moiety (Table 1, entry 7) to produce the cyclization products. In contrast to the results of $AuCl_3$-catalyzed reaction,[8] alkyne of **1d** bearing a TMS group reacted smoothly with I_2 to afford 2,3-diiodo-substituted furan **2j** in 60% yield in which desilylation−iodination easily occurred under the standard reaction conditions. The appearance of a methyl substituent on the alkene moiety in **1e** did not influence the efficiency of this reaction (Table 1, entry 11), in which the corresponding product **2k** was formed in 64% yield. When 2-alkynylcyclopentenone **1f** was employed, the cyclopenta[*b*]furan

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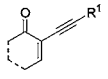
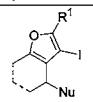
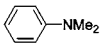
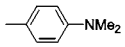
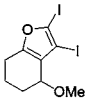
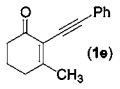
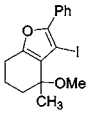
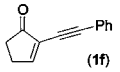
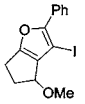
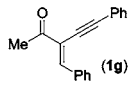
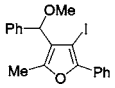
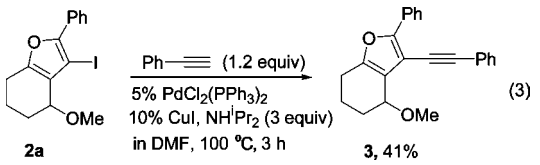
Table 1. Iodocyclization of 2-(1-Alkynyl)-2-alken-1-ones

entry	substrate	nucleophile	products		yield(%)[a]
					
1	R^1=Ph, (**1a**)	MeOH	Nu=MeO	**2a**	94
2	(**1a**)	PhOH	PhO	**2b**	80
3	(**1a**)			**2c**	99
4	(**1a**)			**2d**	88
5	(**1a**)			**2e**	91[b]
6	R^1=*p*-Tol, (**1b**)	MeOH	MeO	**2f**	91
7	 (**1c**)	MeOH	MeO	**2g**	47
8	(**1a**)		CH_2COPh	**2h**	47[c]
9	(**1a**)			**2i**	60
10	R^1=TMS, (**1d**)	MeOH		**2j**	60[c]
11	 (**1e**)	MeOH		**2k**	64
12	 (**1f**)	MeOH		**2l**	59[c]
13	 (**1g**)	MeOH		**2m**	50

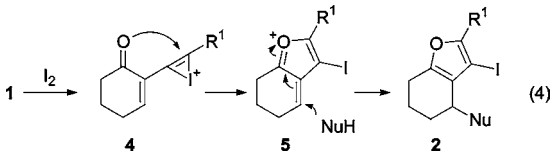
[a] Unless noted, all of the reaction was carried out using I_2 (1.1 equiv) and K_3PO_4 (1.1 equiv) at room temperature for 30 min. [b] Two isomers were obtained in the ratio of 1:1. [c] The reaction was carried out for 3 h using I_2 (3 equiv) and K_3PO_4 (3 equiv).

derivative **2l** was obtained in 59% yield. Acyclic 2-alken-1-one **1g** also underwent a smooth annulation reaction with MeOH to produce furan **2m** in 50% yield. The utility of 3-iodofurans produced by this chemistry as useful synthetic intermediate for further elaboration was briefly investigated by Pd-catalyzed Sonogashira reaction of **2a**, which afforded alkynylated product **3** in 41% yield.



(3)

On the basis of the results obtained above, a plausible reaction mechanism is shown in eq 4,[16] which involves (i) cyclic iodonium ion **4** formation through coordination of the triple bond with an iodine cation; (ii) the anti attack of the oxygen onto the iodonium ion led to the formation of intermediate **5**; (iii) 1,4-addition of a nucleophile to the C−C double bond to afford furan derivative **2**.



(4)

In summary, we have demonstrated that electrophilic cyclization of 2-(1-alkynyl)-2-alken-1-ones[17] with a various nucleophiles using the I_2/K_3PO_4 system yields highly substituted halofurans in good to excellent yields under extremely mild conditions. The iodo derivatives are potential synthetic intermediates for amplification of molecular complexity. Further investigation into the scope and limitations of this electrophilic cyclization is underway.

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

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