Electrophilic Cyclization of 2-(1-Alkynyl)-2-alken-1-ones Using the I₂/K₃PO₄ System: An Efficient Synthesis of Highly Substituted Iodofurans

Yuanhong Liu* and Shaolin Zhou

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Republic of China

yhliu@mail.sioc.ac.cn

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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 methods³ or by transition-metal-catalyzed reactions, including

cyclization of allenyl ketones⁴ 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 AuCl₃-catalyzed cyclization of 2-(1alkynyl)-2-alken-1-ones leading to substituted furans⁸ (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



In this paper, we report the cyclization of 2-(1-alkynyl)-2-alken-1-ones¹² 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 CH₂Cl₂ with methanol, iodine, and carbonate bases, such as NaHCO₃ (15 h, 51%) or Na₂CO₃ (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.



The use of organic base of Et₃N 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 I₂, and 1.1 equiv of K₃PO₄ in CH₂-Cl₂ stirred at room temperature for an appropriate time. The results are summarized in Table 1. In most cases, the ringclosure 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 I₂/K₃PO₄based 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 AuCl₃-catalyzed reaction,⁸ alkyne of 1d bearing a TMS group reacted smoothly with I₂ 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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 a Unless noted, all of the reaction was carried out using I₂ (1.1 equiv) and K₃PO₄ (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 I₂ (3 equiv) and K₃PO₄ (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.



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**.



In summary, we have demonstrated that electrophilic cyclization of 2-(1-alkynyl)-2-alken-1-ones¹⁷ 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 ¹³C 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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