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# A Facile Zr-Mediated Approach to (*Z*)-Enynols and Its Application to Regio- and Stereoselective Synthesis of Fully Substituted Dihydrofurans

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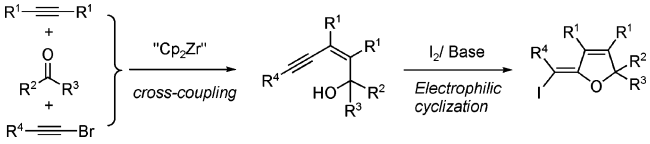


Efficient synthetic approaches to stereodefined (Z)-enynols have been developed through zirconium-mediated cross-coupling reactions of three different components involving alkyne, ketone, and alkynyl bromide in a one-pot procedure. The subsequent electrophilic cyclization of a wide variety of (*Z*)-enynols affords fully substituted (*Z*)-5-(1-iodoylidene)-2,5-dihydrofurans with high regio- and stereoselectivity under mild reaction conditions.

Oxygen-containing heterocycles and their analogues widely occur as structural subunits in numerous natural products, which have displayed interesting biological activities and find applications in pharmaceutical use.[1] Furthermore, substituted heterocycles, in particular, halogen-containing ones, are of significant interest since they are useful and versatile synthetic intermediates for further structural elaboration. Electrophile-promoted cycloaddition of unsaturated compounds has proven to be a powerful synthetic route to the wide variety of halogenated heterocyclic compounds.[2] However, the electrophilic cyclization performed on acetylenic compounds has been far less studied, although alkynes have been frequently employed in transition-metal-catalyzed inter- or intramolecular annulations to produce fruitful results for the synthesis of carbo- and heterocycles.[3] Most of the recent reports focused on arylalkynes bearing ortho-related heteroatomic nucleophiles, which provided efficient approaches to benzofused heterocycles such as benzothiophenes,[4a,b] benzo[*b*]furans,[4c,d] isoquinolines,[4e] quinolines,[4f] isochromenes,[4g,h] furopyridines,[4i] indoles,[4j,k] isoindolin-1-ones,[4l] and so on.[4] Enynes bearing nucleophilic substituents such as −OH, −NHR, and SR groups would represent an important class of suitable substrates for this strategy due to the structural analogy with arylalkynes; however, only limited reports concerning electrophilic cyclization have been presented in the literature by employing enyne derivatives.[5] It is known that (*Z*)-enynols undergo transition-metal-catalyzed transformations to form substituted furans.[6] The preparation of (*Z*)-enynols are usually achieved through multistep transformations involving Pd/Cu-catalyzed coupling of the terminal alkynes with vinylic halides, addition of alk-1-ynes to vinyl ketones followed by acid-catalyzed allylic isomerization, reduction of methyl (*Z*)-2-en-4-ynoates etc.[6a,c] Nevertheless, enhancing the efficiency of the synthesis of these compounds is still highly attractive. In our ongoing efforts[7] to maximize the molecular complexity from simple building blocks using zirconium,[8] we found that (*Z*)-2-en-4-yn-1-ols were readily constructed by a one-pot, three-component reaction. This strategy offered the advantage of the efficient route for substituted

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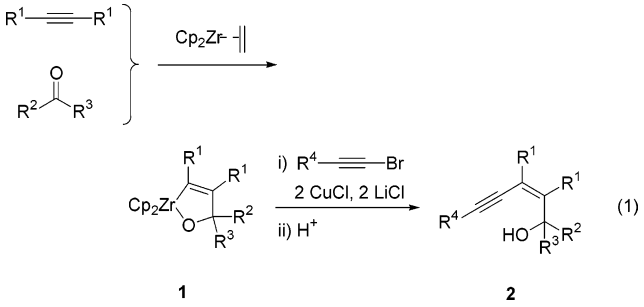
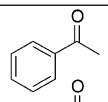
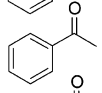
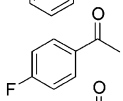
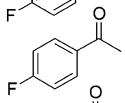
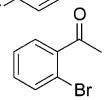
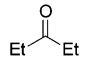
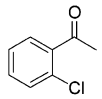
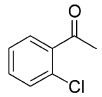
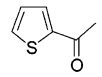
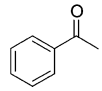
(*Z*)-enynols with a tertiary alcoholic group, which enabled us to develop convenient protocol for the synthesis of highly substituted 5-(1-iodoylidene)-2,5-dihydrofurans with high regio- and stereoselectivity.

Alkynes undergo selective intermolecular coupling with aldehydes or ketones using zirconocenes.[9] The hydrolysis of the thus-formed oxazirconacyclopentene **1** with aqueous HCl solution affords allylic alcohols in good to excellent yields. Takahashi recently reported a new pathway for the formation of 2,5-dihydrofuran derivatives by the reaction of oxazirconacyclopentenes **1** with propynoates.[9b] We envisioned that the oxazirconacycles could be converted to (*Z*)-enynols by further applications of these cross-coupling reactions. The straightforward way is to develop a method for selective alkynylation of Zr−C bond of oxazirconacyclopentenes **1**. This was solved by the coupling of zirconacycle **1** with an alkynyl bromide (eq 1).




It was found that **1** did not react with alkynyl bromide directly. Copper-catalyzed or -mediated carbon−carbon bond formation reactions of zirconacycles have been reported, and transmetalation of Zr−C bonds to Cu−C bonds has proven to be an effective methodology for activation of Zr−C bonds.[10] Treatment of oxazirconacycle **1e** ($R^1$ = Ph, $R^2$ = *o*-$BrC_6H_4$, $R^3$ = Me) with 2 equiv of 1-hexynyl bromide and 2 equiv of CuCl at room temperature and stirring the mixture for 24 h afforded (*Z*)-enynols **2e** in 51% yield after hydrolysis. It should be noted that addition of 2 equiv of LiCl resulted in a cleaner reaction process and reduced reaction time (12 h). In the presence of LiCl, **2e** was obtained in higher isolated yield (69%). This result can be explained by the fact that the LiCl salt may facilitate the transmetalation of Zr−C bond to Cu−C bond and stabilize the organocopper species generated in the reaction solution.[11] The representative reactions with various alkynyl bromide are listed in Table 1. Alkynyl bromide bearing alkyl or aryl substituents reacted very well with oxazirconacycles to afford enynols **2** in 57−92% yields. A wide range of aromatic ketones could be used, especially with halogenated aromatic ketones, affording the corresponding enynols in good to high yields. 2-Acetylthiophene could also be applied in this reaction to give **2i** in 57% isolated yield. When an aliphatic ketone such as 3-pentanone was subjected to the reaction, a prolonged reaction time was required (24 h) to afford **2f** in 71% yield.

**TABLE 1. Formation of (*Z*)-Enynols from Three-Component Reactions Mediated by Zirconium**

| Alkyne | Ketone | Alkynyl Bromide | Product | Yield (%)[a] |
|---|---|---|---|---|
| Ph—≡—Ph |  | Bu—≡—Br | **2a** | (60)[b] |
| Ph—≡—Ph |  | Ph—≡—Br | **2b** | 71 (56) |
| $C_3H_7$—≡—$C_3H_7$ |  | Ph—≡—Br | **2c** | 85 (70) |
| Ph—≡—Ph |  | Bu—≡—Br | **2d** | 70 (64)[b] |
| Ph—≡—Ph |  | Bu—≡—Br | **2e** | 83 (69) |
| Ph—≡—Ph |  | Bu—≡—Br | **2f** | 71 (51)[c] |
| Ph—≡—Ph |  | Ph—≡—Br | **2g** | (74)[b,c] |
| Ph—≡—Ph |  | Bu—≡—Br | **2h** | 92 (76)[b] |
| Ph—≡—Ph |  | Bu—≡—Br | **2i** | (57) |
| Bu—≡—Bu |  | *p*-$CH_3OC_6H_4$—≡—Br | **2j** | (66) |

[a] GC yields. Isolated yields are given in parentheses. Unless noted, all of the reactions were done at room temperature for 12 h using alkynyl bromide (2 equiv), CuCl (2 equiv), and LiCl (2 equiv). [b] Alkynyl bromide (1 equiv), CuCl (1 equiv), and LiCl (2 equiv) were used. [c] The reaction was performed for 24 h.

With (*Z*)-enynols **2** in hand, we were interested in exploring the feasibility of using **2** in electrophilic cyclization reactions. We began our investigation with enynol **2a** ($R^1$ = Ph, $R^2$ = Ph, $R^3$ = Me, $R^4$ = Bu) bearing alkyl group at C-5 and a tertiary alcohol group at C-1. The reaction of **2a** with $I_2$ was done first in solvents such as $CH_2Cl_2$ and $CH_3CN$ which were frequently used for iodocyclization in the presence of $NaHCO_3$ as base. However, only sluggish reaction mixture was observed. After many efforts, we were delighted to find that iodocyclization proceeded smoothly and provided a >99% NMR yield of the 5-ylidene-2,5-dihydrofuran derivative **3a** in THF solution with $K_3PO_4$ as base. The results for

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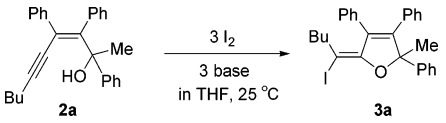
**TABLE 2. Effect of Base for the Iodocyclization Reaction**




| base | time (h) | yield[a] (%) | base | time (h) | yield[a] (%) |
|---|---|---|---|---|---|
| | 6 | 24 | $K_3PO_4$ | 1 | >99 |
| $Na_2CO_3$ | 8 | 71 | $NaOCO_2CH_3$ | 4 | >99 |
| $NaHCO_3$ | 6 | 75 | KO$^t$Bu | 9 | 56 |
| $KHCO_3$ | 18 | 18 | $NEt_3$ | 20 | 10 |
| KOH | 3 | 37 | pyridine | 12 | 78 |

[a] NMR yields.

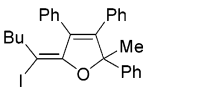
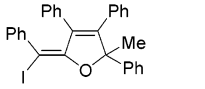
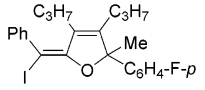
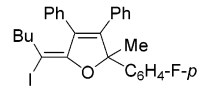
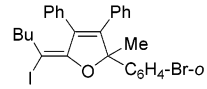
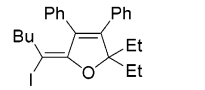
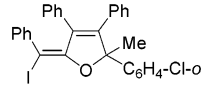
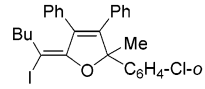
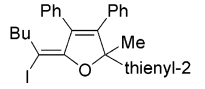
optimization of this electrophilic cyclization process are summarized in Table 2. When no base was employed, only 24% of product **3a** was obtained. The addition of carbonate bases such as $Na_2CO_3$, $NaHCO_3$, and $KHCO_3$ increased the yield of **3a** to 71, 75, and 79% NMR yields along with the formation of several side products, which was difficult to be separated from the main product. When a stronger base, KO$^t$Bu was used, 56% yield of **3a** was observed. The use of organic base such as $Et_3N$ and pyridine resulted in the formation of **3a** in 10% and 78% yields, respectively. The presence of $K_3PO_4$ was crucial for a clean, high-yielding reaction within short reaction time (1 h). It was suggested that $K_3PO_4$ would neutralize the produced HI of iodocyclization and generate $K_2HPO_4$, while using carbonate bases would produce $H_2O$. The $H_2O$ generated might lead to the formation of side products.[4e] Accordingly, using $NaOCO_2CH_3$ as reported by Larock et al. in isoquinoline formation reaction[4e] also afforded the desired product in high yield (>99%).

Based on the above optimization results, we chose the following reaction conditions: 3 equiv of $I_2$ and 3 equiv of $K_3PO_4$ or $NaOCO_2CH_3$ in THF stirred at room temperature for an appropriate amount of time. The results are summarized in Table 3.

The alkyne moiety in enynols **2** bearing an aromatic ring as well as alkyl substituent all reacted very well to provide the 5-*exo*-*dig* cyclization product in 66−86% yields. The effect of substitution on α-carbon of alcoholic group in **2** has also been examined: enynol **2f** bearing two alkyl group on α-carbon of alcoholic group (entry 6) required increased amount of base (6 equiv) and a prolonged reaction time (12 h). Bulky substrates, such as **2g** bearing the *o*-chlorophenyl group at C-1 and phenyl group at the end of the alkyne moiety, tend to hinder cyclization. A stronger reaction condition involving 6 equiv of $I_2$ and 6 equiv of base was required, and the product of **3g** still could be formed in 73% yield within 3 h.

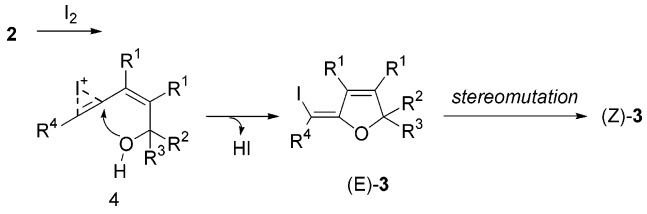
It is interesting to note that in all cases, only 5-*exo*-*dig* iodocyclization occurred and stereoisomerically pure compounds (*Z*)-**3** were found to be the only reaction products, while the regioisomers of pyran derivative derived from 6-endocyclization and the stereoisomer of (*E*)-**3** were not observed. The observed selectivity are rare in electrophilic cyclization reactions. The structure of dihydrofurans were unequivocally confirmed by single-crystal analysis of **3g** and **3h**. These results clearly showed five-membered oxygen heterocycles and the (*Z*)-

**TABLE 3. Synthesis of Highly Substituted Stereofined 5-Ylidene-2,5-2*H*-furans**

| Entry | Enynols | Base/Time | Product | | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | **2a** | $K_3PO_4$, 1h |  | (**3a**) | 74 |
| 2 | **2b** | $NaOCO_2CH_3$, 1h |  | (**3b**) | 66 |
| 3 | **2c** | $K_3PO_4$, 8h |  | (**3c**) | 85 |
| 4 | **2d** | $K_3PO_4$, 1h |  | (**3d**) | 82 |
| 5 | **2e** | $K_3PO_4$, 3h |  | (**3e**) | 66 |
| 6 | **2f** | $K_3PO_4$, 12h |  | (**3f**) | 77[b] |
| 7 | **2g** | $NaOCO_2CH_3$, 3h |  | (**3g**) | 73[c] |
| 8 | **2h** | $NaHCO_3$, 4h |  | (**3h**) | 86 |
| 9 | **2i** | $NaOCO_2CH_3$, 3h |  | (**3i**) | 76[b] |

[a] Isolated yields. [b] 6 equiv of base was used. [c] 6 equiv of $I_2$ and 6 equiv of $I_2$ base were used.

**SCHEME 1**




configuration of **3**. On the basis of the above observations, a possible reaction mechanism is proposed in Scheme 1, which may involve the following steps: (i) Cyclic iodonium ion **4** was formed through coordination of the triple bond with iodine cation. (ii) Anti attack of the oxygen of alcohol group onto iodonium ion led to the formation of (*E*)-**3**. In intermediate **4**, more of the partial positive charge caused by iodine coordination is located on the alkyne carbon closed to the substituted double bond moiety, since it stabilizes a carbocation much better. Thus, a 5-*exo*-*dig* cyclization resulted. (iii) (*E*)-**3** underwent stereomutation in the presence of $I_2$ to give the thermodynamically more stable (*Z*)-product **3**. Similar iodine-promoted isomerization of vinyl iodide compounds was reported previously.[12]

In summary, we have succeeded in developing an efficient, general, and one-pot procedure to synthesize

stereodefined (*Z*)-enynols through zirconium-mediated cross-coupling of alkyne, ketone, and alkynyl bromide. The iodocyclization of a wide variety of (*Z*)-enynols affords fully substituted 5-ylidene-2,5-dihydrofurans with high regio- and stereoselectivity under mild reaction conditions. This methodology provided a highly efficient route to stereodefined oxygen heterocycles from common starting materials. We are currently exploring the new synthetic potential of electrophilic cyclization reactions.

## Experimental Section

**Typical Experimental Procedure for the Preparation of Enynol 2a.** To a solution of $Cp_2ZrCl_2$ (0.365 g, 1.25 mmol) in THF (5 mL) was added EtMgBr (1.0 M THF solution, 2.5 mmol) at −50 °C. After the mixture was stirred for 1 h at the same temperature, diphenylacetylene (0.18 g, 1 mmol) was added, and the reaction mixture was warmed to 0 °C and stirred for 3 h. Acetophenone (0.12 g, 1 mmol) was added, and the reaction mixture was heated to 50 °C for 1 h. Then, to the above reaction solution containing oxazirconacyclopentene **1a** were added 1-hexynyl bromide (0.32 g, 2 mmol), CuCl (0.20 g, 2 mmol), and LiCl (0.08 g, 2 mmol) at room temperature. After being stirred at room temperature for 12 h, the reaction mixture was quenched with 3 N HCl solution and extracted with diethyl ether. The extract was washed with $NaHCO_3$, water, and brine. The solvent was evaporated in vacuo, and the residue was purified by chromatography on a $Al_2O_3$ column (petroleum ether/ethyl acetate =15:1) to afford 245 mg (64%) of product as a yellow oil.

**General Procedure for Electrophilic Cyclization of Enynols 2.** To a solution of enynol **2** (0.2 mmol) in 1.5 mL of THF were added $K_3PO_4$ (0.6 mmol) and $I_2$ (0.6 mmol) at 0 °C. After 5 min, the above suspension was warmed to room temperature and stirred for an appropriate amount of time. The reaction mixture was then diluted with ethyl acetate, washed with saturated $Na_2S_2O_3$ solution, dried ($Na_2SO_4$), and filtered. The solvent was evaporated under reduced pressure, and the product was isolated by chromatography on an $Al_2O_3$ column.

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**Supporting Information Available:** Experimental details and characterization data of compounds **2a**−**j**, **3a**−**i**, and crystallographic data of **3g**,**h**. 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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(12) (a) Takahashi, T.; Kondakov, D. Y.; Xi, Z.; Suzuki, N. *J. Am. Chem. Soc.* **1995**, *117*, 5871. (b) Reference 4b. (c) Reference 5a.