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Reaction of Oxazirconacyclopentenes with Propynoates. A New Pathway for the Formation of 2,5-Dihydrofuran Derivatives

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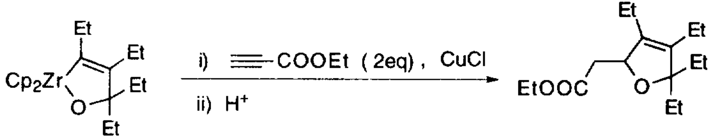
Abstract: Oxazirconacyclopentenes, which were easily prepared from Cp_2ZrEt_2, alkynes and ketones, reacted with propynoate in the presence of CuCl to give 2,5-dihydrofurans after hydrolysis.

Recently, we have reported the first example of 1,1-cycloaddition of zirconacyclopentadienes to propynoates affording five-membered ring compounds.[1] In this reaction, two new carbon-carbon bond formations proceeded at the terminal carbon of the triple bond of the propynoate without CuCl. This was in sharp contrast to the case with CuCl which gave 1,2-cycloaddition of zirconacyclopentadienes to substituted propynoates forming benzene derivatives.[2] Our attention was turned to the reactions of zirconaheterocycles such as oxazirconacyclopentenes, which are easily prepared by the reaction of zirconacyclopentenes with ketones.[3] The expected products, 2,5-dihydrofurans, are useful intermediates for organic synthesis[4,5] and also comprise a structural unit of some natural compounds.[6] In this paper we report the reaction of oxazirconacyclopentenes with propynoate in the presence of CuCl which gives 2,5-dihydrofuran derivatives as shown in eq (1).



1a

2a: 92% yield

(1)

Typically, to a solution of oxazirconacyclopentene **1a**, which was prepared in THF (5 mL) from Cp_2ZrCl_2 (292 mg, 1 mmol), EtMgBr (1M THF solution, 2 mL, 2 mmol), 3-hexyne (1 mmol) and 3-pentanone (1 mmol) according to our procedure,[3] was added ethyl propynoate (196 mg, 2 mmol) and CuCl (198 mg, 2 mmol). The reaction mixture was stirred at room temperature for 3h, quenched with 3N HCl, and extracted with Et_2O. GC analysis using a hydrocarbon as an internal standard indicated that **2a** was formed in 92% yield. The extract was washed with NaCl aq, dried over $MgSO_4$, and concentrated *in vacuo*. Column chromatography on silica gel (4/1 hexane/Et_2O) afforded 188 mg (70%) of **2a** as a colorless liquid.

The results are summarized in Table 1. Reaction of both monocyclic (entries 1-4) and spirocyclic (entries 5-7) oxazirconacyclopentenes with ethyl propynoate gave good to high yields of the corresponding 2,5-dihydrofuran derivatives. The formation of two regioisomers (entry 4) was observed since **1d** contains the

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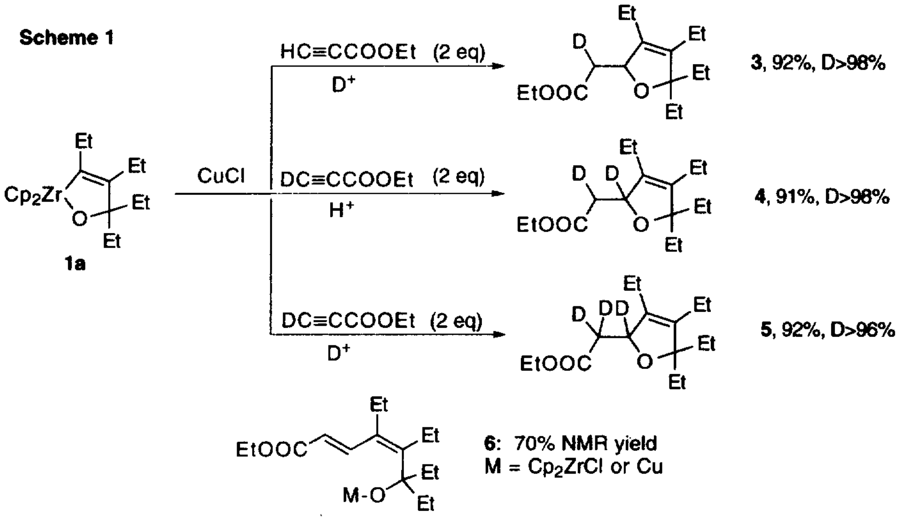
regioisomers of the Me and Ph groups. In the case of unsymmetrically substituted oxazirconacyclopentenes (entry 8), a 1.1:1 mixture of diastereoisomers was formed.

It is noteworthy that without CuCl this cyclization reaction giving dihydrofurans did not proceed and that in the presence of CuCl the products were 2,5-dihydrofurans but not the six-membered ring compounds that were the products for the reaction of zirconacyclopentadienes in the presence of CuCl. This is due to the different reactivity of the carbon attached to zirconium in oxazircoancyclopentenes. Substituted propynoates (internal alkynes) did not react with **1a**.

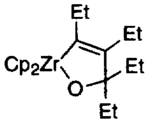
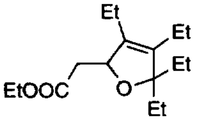
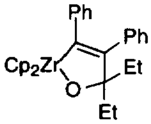
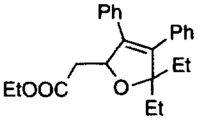
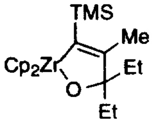
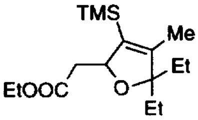
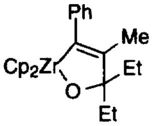
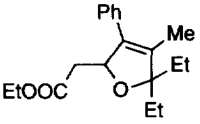
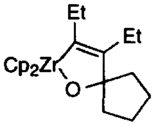
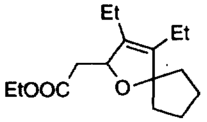
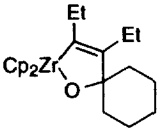
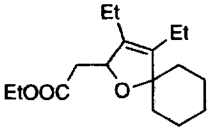
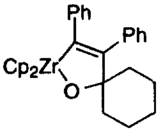
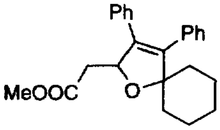
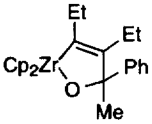
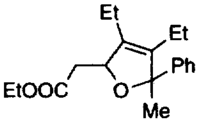
In order to elucidate the reaction mechanism we carried out the following procedures: a) quenching the reaction mixture with DCl instead of 3N HCl, b) performing the reaction with a deuterium labeled substrate (ethyl [3-^{2}H]-propynoate),[7] and c) monitoring the reaction mixture by NMR. The reaction with propynoate quenched with DCl afforded monodeuterated compound **3**. The reaction with deuterated propynoate quenched with HCl afforded dideuterated compound **4** and the reaction with deuterated propynoate quenched with DCl afforded trideuterated compound **5**. Moreover, the monitoring of the reaction by NMR indicated the formation of the open-chain intermediate **6**. The ^{1}H NMR spectrum of **6** showed two characteristic doublets at 5.90 and 8.05 with a coupling constant of 15.9 Hz assignable to a *trans* double bond having a carboxylic group. The corresponding two sp^2 carbons appeared at 116.02 and 144.21 ppm in its ^{13}C NMR spectrum. The formation of **4** and **5** clearly indicates that during the course of the reaction there was deuterium transfer from [3-^{2}H]-propynoate to some intermediate and it also explained why it was necessary to use at least two equivalents of propynoate with respect to the oxazirconacyclopentene to achieve high yields of the products. The formation of **6** shows that the cyclization to give the dihydrofuran derivative proceeds after hydrolysis, i.e., nucleophilic addition of alcohol to the activated double bond.

Scheme 1



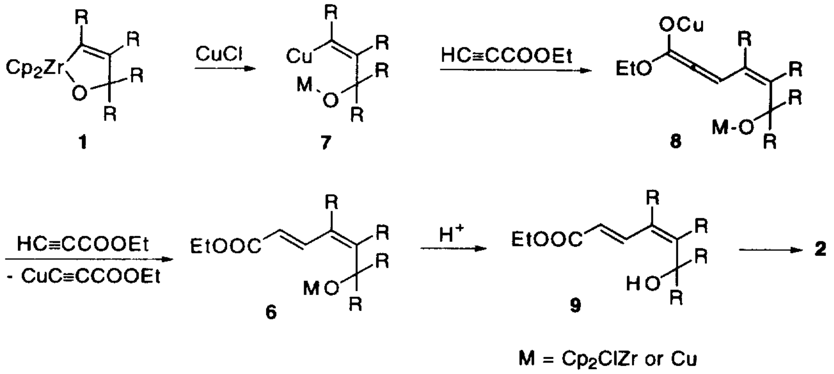
Based on the results obtained here, the following reaction mechanism can be proposed for the formation of dihydrofurans (Scheme 2). In the first step the Zr-C bond of **1** is transmetalated to the Cu-C bond to give **7**. It is not clear whether only the Zr-C bond is transmetalated, or also the Zr-O bond. Intermediate **7** then adds to the triple bond of propynoate to give enolate **8**. Enolate **8** is hydrolyzed by acidic hydrogen of another molecule of propynoate to give open-chain intermediate **6**. The cleavage of enolate by acidic hydrogen of propynoate was already observed in a similar reaction.[1] Hydrolysis with HCl gives alcohol **9** that undergoes intramolecular Michael reaction and affords the dihydrofuran derivative **2**.

Table 1. Reaction of oxazirconacyclopentenes with 2 equiv of ethyl propynoate in the presence of CuCl.

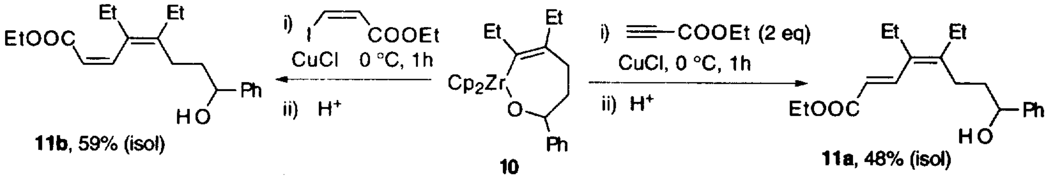
Entry	Zirconacycle		Time (h)	Product[a]		Yield (%)[b]
1		(1a)	3		(2a)	92 (70)
2		(1b)	9		(2b)	82 (61)
3		(1c)	12		(2c)	57 (50)
4		(1d)[c]	12		(2d)[d]	66(43)
5		(1e)	12		(2e)	43 (35)
6		(1f)	12		(2f)	67 (51)
7		(1g)	12[e]		(2g)	52 (41)
8		(1h)	12		(2h)[f]	71 (51)

[a] Products were obtained after hydrolysis. [b] GC yield, Isolated yields are given in parentheses.
[c] A 1:1 mixture of two regioisomers. [d] A 1.5:1 mixture of two regioisomers; Major isomer is shown.
[e] Methyl propynoate was used. [f] A 1:1 mixture of two diastereoisomers.

Scheme 2



Oxazirconacycloheptene **10**, prepared by the reaction of zirconacyclopentenes with carbonyl compounds at 0 °C,[8] also reacted with ethyl propynoate. It is interesting to note that, however, in this case only ***trans-cis*** dienoate **11a** was formed and that the formation of five- or seven-membered heterocycles by 1,4 or 1,6-conjugate addition was not observed. It is also interesting to report that the reaction of **10** with iodopropenoate afforded only *cis-cis* dienoate **11b** as shown below.



References and notes

1. Takahashi, T.; Sun, W.-H.; Xi, C.; Kotora, M. *Chem. Commun.* **1997**, 2069.
2. (a) Takahashi, T.; Kotora, M.; Xi, Z.; *J. Chem. Soc., Chem.Commun.* **1995**, 1503. (b) T. Takahashi, T.; Xi, Z.; Yamazaki, A.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1998**, *120*, 1672.
3. (a) Takahashi, T.; Kageyama, M.; Denisov, V.; Hara, R.; Negishi, E. *Tetrahedron Lett.* **1993**, *34*, 687. (b) Takahashi, T.; Xi, C.; Xi, Z.; Kageyama, M.; Fischer, R.; Nakajima, K.; Negishi, E. *J. Org. Chem.*, **1998**, *63*, 6802.
4. (a) Marshall, J.A.; Pinney, K. *J. Org. Chem* **1993**, *58*, 7180. (b) Marshall, J.A.; Yu, B. *J. Org. Chem* **1994**, *59*, 324. (c) Paolucci, C.; Musiani, L.; Venturelli, F.; Fava, A. *Synthesis* **1997**, 1415.
5. (a) Tenanglia, A.; Le Brazidec, J.-T. *Chem. Commun.* **1996**, 1663. (b) Hojo, M.; Aihara, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* **1996**, *37*, 9241. (c) Shieh, S.-J.; Fan, J.-S.; Chandrasekharam, M.; Liao, F.-L.; Wang, S.-L.; Liu, R.-S.*Organometallics* **1997**, *16*, 3987. (d) Doyle, M.P.; Forbes, D.C.; Protopopova, M.N.; Stanley, S.A.; Vasbinder, M.M.; Xavier, K.R. *J. Org. Chem* **1997**, *62*, 7210. (e) Aurrecoechea, J.M.; Solay, M. *Tetrahedron* **1998**, *54*, 3851. (f) Schieweck, F.; Altenbach, F.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 403.
6. (a) Kupchan, S.M.; Davies, V.H.; Fujita, T.; Cox, M.R.; Restivo, R.J.; Bryan, R.F.*J. Org. Chem* **1973**, *38*, 1853. (b) Semple, J.E.; Wang, P.C.; Lysenko, Z.; Joullie, M.M. *J. Am. Chem. Soc.* **1980**, *102*, 7505. (c) Deli, J.; Molnar, P.; Toth, G.; Baumeler, A.; Eugster, C.H. *Helv. Chim. Acta* **1991**, *74*, 819.
7. Townsend, C.A.; Brown, A.M.; Nguyen, T.T. *J. Am. Chem. Soc.* **1983**, *105*, 919.
8. Coperet, C.; Negishi, E.; Xi, Z.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 695.