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One-pot four-component synthesis of tetrahydrofuran derivatives involving an alkyne, an ethylene and two aldehydes via CuCl-mediated reactions of oxazirconacyclopentenes with aldehydes

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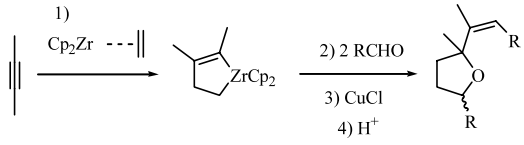
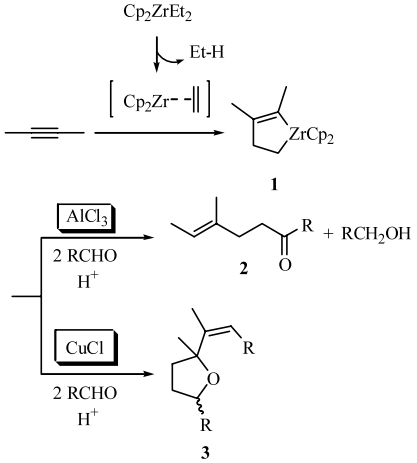
Abstract—In the presence of 1 equiv. of CuCl, the reaction of zirconacyclopentenes with 2 equiv. of aldehydes from −78°C to room temperature afforded tetrahydrofuran derivatives in good isolated yields upon hydrolysis with aqueous 3N HCl; oxazirconacycloheptenes, generated in situ from zirconacyclopentenes with one aldehyde, was found to be the reactive intermediate.

Tetrahydrofuran skeletons are frequently found in natural products.[1] Thus, development of synthetically useful methods for the preparation of THF derivatives is of great interest.[2–6] In this paper, we report the first one-pot synthesis of THF derivatives from four components via a novel CuCl-mediated reaction of oxazirconacycloheptenes with aldehydes (Scheme 1).

Recently, we reported an $AlCl_3$-mediated reaction of zirconacyclopentenes **1** with aldehydes.[7] Oppenauer-type oxidation took place to give homoallylketones **2** and alcohols.[7] Only one of the two aldehydes was incorporated into the product. The second molecule of aldehyde was reduced to an alcohol. Surprisingly, as shown in Scheme 2, when the additive was changed from $AlCl_3$ to CuCl, tetrahydrofuran derivatives (THF derivatives for short) **3** were obtained in good yields. No formation of homoallylketones **2** was observed in these reactions.



Scheme 1. Formation of THF derivatives from four components in one-pot.



Scheme 2. Totally different products were generated only by change of additives.

Keywords: aldehydes; four-component synthesis; tetrahydrofuran derivatives; zirconacyclopentenes; oxazirconacycloheptenes; CuCl.

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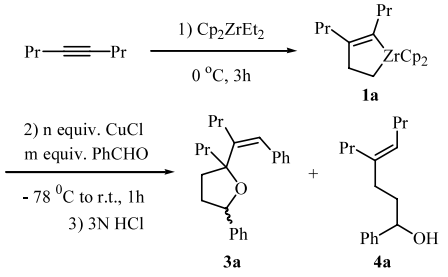
Reaction of 4-octyne with diethylzirconocene (Cp_2ZrEt_2) affords zirconacyclopentene **1a** in more than 95% yield, as reported by Takahashi.[8] After addition of CuCl and aldehydes to a THF solution of **1a** at −78°C, the reaction temperature was slowly increased to room temperature and the mixture was stirred at the temperature for 1 h. Hydrolysis of the reaction mixture with either aqueous 3N HCl or saturated aqueous $NaHCO_3$ afforded the THF derivative **3a** as a mixture of two isomers in a ratio of 2:1 (Table 1). The stereochemistry of the product was determined by NOE measurement.

As given in Table 1, though best yield of **3a** was obtained when 1 equiv. of CuCl and 2 equiv. of benzaldehydes were used, the yield was not satisfactory. In addition to **3a**, formation of alcohol **4a** was also observed. As given in entry 1 and entry 4, alcohol **4a** was formed as the major product. The formation of alcohol **4a** can be rationalized by generation of the intermediate oxazirconacycloheptene **5a** (Scheme 3), which upon hydrolysis gives rise to alcohol **4a**.[9]

In order to optimize the reaction procedure to improve the yields of THF derivatives, we tried to start with oxazirconacycloheptenes **5**.[9] As expected, the reaction became much cleaner and afforded the products in better yields. When 1 equiv. of benzaldehyde was added to zirconacyclopentene **1a**, the oxazirconacycloheptene **5a** was generated in situ in the first step (Scheme 4).[9] Addition of only CuCl to the reaction mixture of **5a** did not afford any formation of **3a**; the corresponding alcohol **4a** was obtained as the only product. However, addition of CuCl and 1 equiv. of benzaldehyde to the reaction mixture of **5a** gave **3a** as a 2:1 mixture in 63% GC yield (Scheme 4).

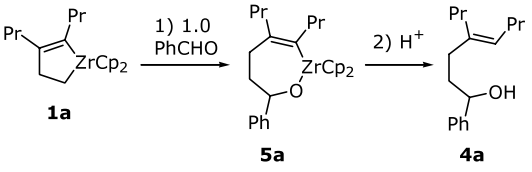
As shown in Scheme 5, if 2 equiv. of benzaldehyde were added in the first step, addition of only CuCl to the reaction mixture of **5a** did afford **3a** in 71% GC yield after hydrolysis with aqueous 3N HCl. These experiments demonstrate that oxazirconacycloheptenes **5** are the reactive intermediates. For the sake of convenience,

Table 1. Effects of amounts of CuCl and aldehydes on the yields of THF derivatives

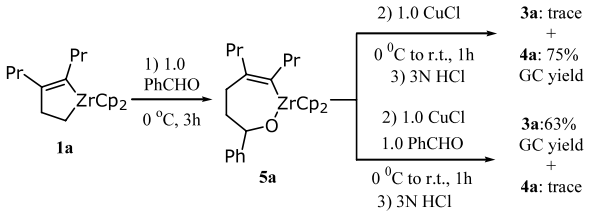


Entry	CuCl (n)	PhCHO (m)	Yield of **3a**/%[a]	Yield of **4a**/%[b]
1	1	1	7	23
2	1	2	43 (30)	18 (10)
3	1.2	2	42	7
4	2	1	6	11

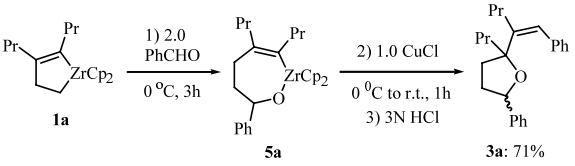
[a] A mixture of two isomers in 2:1. Combined GC yields. Combined isolated yields are given in parentheses.
[b] GC yields. Isolated yields are given in parentheses.



Scheme 3.

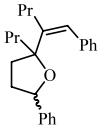
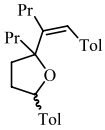
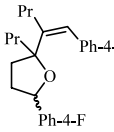
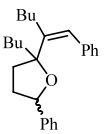


Scheme 4.



Scheme 5.

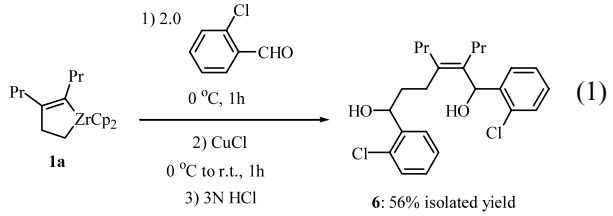
Table 2. Formation of THF derivatives from two aldehydes, one alkyne and one ethylene

Entry	Alkyne	Aldehyde	Product **3**		Yield of **3**/%[a]
1	Pr—≡—Pr	PhCHO		**3a**[b]	71 (44)
2	Pr—≡—Pr	TolCHO		**3b**[c]	(42)
3	Pr—≡—Pr	4-F-PhCHO		**3c**[d]	(54)
4	Bu—≡—Bu	PhCHO		**3d**[e]	(48)

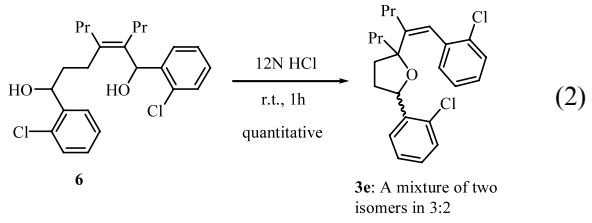
[a] Combined GC yields. Combined isolated yields are given in parentheses. [b] Two isomers in 2:1. [c] Two isomers in 1:1. [d] Two isomers in 2:1. [e] Two isomers in 3:2.

the procedure shown in Scheme 5 was used to obtain products listed in Table 2. Aromatic aldehydes could generally afford THF derivatives in good yields. When aliphatic aldehydes were used, although the corresponding oxazirconacycloheptenes **5** could be formed cleanly,[9] the next reaction step involving CuCl was messy.[10]

Interestingly, when 2-chlorobenzaldehyde was used, 2-hexen-1,6-diol **6** was obtained as the only product after the reaction mixture was hydrolyzed with aqueous 3N HCl (Eq. (1)). This diol **6** could be quantitatively transformed to the THF derivative **3e** when treated with aqueous 12N HCl at room temperature for 1 h (Eq. (2)).[11,12] As one of possible mechanisms for the formation of THF derivatives, acid-promoted cyclization of in situ generated 2-hexen-1,6-diols **6** is proposed.[12] It is noteworthy that the THF derivative **3e** was also obtained as a mixture of two isomers in a ratio of 3:2. This result is informative for understanding the reaction mechanism. Formation of the allylic alcohol moiety in **6** is assumed via nucleophilic addition of alkenylcopper to the carbonyl group of an aldehyde. Such direct addition reaction is unprecedented.[13]



(1)



(2)

In summary, this paper reports the first synthesis of THF derivatives from four components in one-pot (Fig. 1). Further investigation into the reaction mechanism, scope and limitations are under progress.

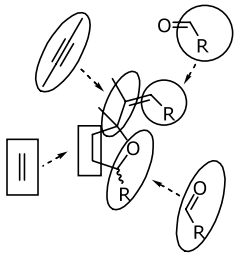


Figure 1.

Acknowledgements

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11. Selected data for **3e**. Light yellow liquid, a mixture of two isomers (3:2). ^{1}H NMR (TMS, $CDCl_3$) $\delta = 0.72$–1.02 (m, 6H), 1.27–2.60 (m, 12H), 5.34–5.42 (m, 1H), 6.66 (s) 6.80 (s) (total 1H), 7.15–7.40 (m, 7H), 7.69 (d, $J = 7.5$ Hz), 7.81 (d, $J = 7.8$ Hz) (total 1H). ^{13}C NMR (TMS, $CDCl_3$), 14.54, 14.69, 14.77, 17.70, 17.97, 22.56, 22.65, 30.97, 31.45, 32.76, 33.14, 35.65, 36.01, 40.62, 42.21, 76.93, 89.09, 89.54, 122.81, 122.96, 126.27, 126.30, 126.70, 126.74, 126.80, 127.23, 127.59, 127.65, 127.88, 127.93, 129.07, 129.16, 129.21, 130.03, 130.14, 131.57, 133.74, 133.78, 137.54, 137.59, 141.41, 141.78, 146.15, 146.93. HRMS calcd for $C_{24}H_{28}O^{35}Cl_2$ 402.1517, found 402.1515.
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