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Tetrahedron Letters 47 (2006) 8621–8623

Tetrahedron Letters

t-BuOK promoted coupling of alkynes and aldehydes: a concise synthetic method of β,γ-unsaturated enones

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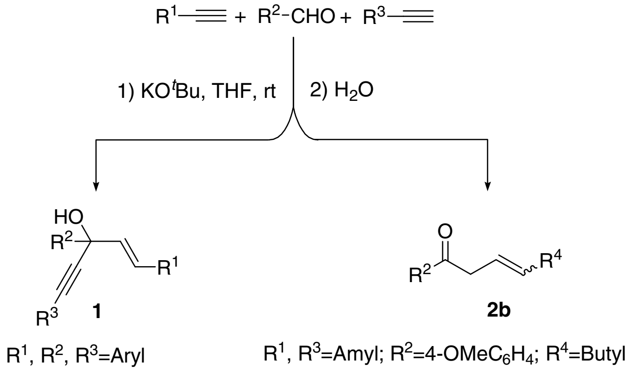
Received 30 June 2006; revised 27 August 2006; accepted 30 August 2006

Abstract—A KO^{t}Bu-promoted coupling reaction of aldehydes and alkynes without a transition-metal catalyst was developed, in which the sequential addition/isomerization processes are involved in one pot. This approach is mild and gives ready access to β,γ-unsaturated enones in moderate to good yields.

The β,γ-unsaturated enones are important and versatile intermediates in organic synthesis[1] and exist widely as functional groups in many natural products.[2] However, their preparations are often difficult, because the non-conjugated β,γ-unsaturated enones tend to isomerize and to form the more stable conjugated α,β-unsaturated enones.[3] Up to now, many synthetic approaches have been developed, such as those based on Claisen rearrangement of α-alkoxy ketone enolates,[4] the oxidation of homoallylic alcohols,[5] the allylation of borolanes,[6] the acylation of olefins,[7] the isomerization of propargylic alcohol with transition-metal catalyst,[8] and the reaction of silylated enaminones with organolithium.[9] However, some of them suffer from tedious procedures that limit their application in practice. In connection with our recent research on the multi-component reaction of aldehydes and alkynes,[10,11] we found that the KO^{t}Bu/THF system could promote a three-component coupling of aromatic aldehydes with alkynes. However, the coupling of 4-methoxybenzaldehyde with 2 equiv of the aliphatic 1-heptyne under the same conditions could not furnish the desired product, but only the β,γ-unsaturated enone **2b** in a 81% yield (Scheme 1). Based on this result, a general and useful method for the synthesis of β,γ-unsaturated enones was developed by using the aliphatic alkyne. In contrast to the other protocols, this approach is mild and gives ready access to β,γ-unsaturated enones in moderate to good yields without a transition-metal catalyst. Herein we wish to report our experimental results.



Scheme 1. Coupling of aromatic aldehyde with aromatic or aliphatic alkyne.

On the basis of the information above, a series of aldehydes and alkynes were tested toward this coupling reaction under an optimized condition (aldehyde, alkyne, and KO^{t}Bu in the mole ratio of 1:1.3:1.8 in THF, rt). As shown in Table 1, various aromatic aldehydes and aliphatic alkynes were effective to realize this coupling reaction, and the reaction afforded the β,γ-unsaturated enones in moderate to good yields. For the aromatic aldehydes, the electronic effects of the substituents on aryl rings strongly affected the yield of the products. In general, electron-rich or electron-neutral aryl aldehydes showed favorable effect on the coupling and gave better yields. But when there was an electron-withdrawing substituent on an aryl aldehyde, such as 4-(trifluoromethyl)benzaldehyde (entry 11), the yield was poor. However, it is puzzling that the reactions of the double

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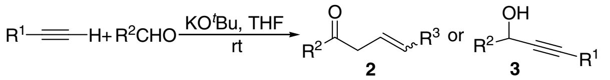
doi:10.1016/j.tetlet.2006.08.109

Table 1. Coupling of alkynes and aldehydes[a]



Entry	R^1	R^2	Product	*Z*/*E*	Yield[b] (%)
1	C_5H_{11}	3-OMeC_6H_4	**2a**	2.3/1	75
2	C_5H_{11}	4-OMeC_6H_4	**2b**	2/1	81
3	C_4H_9	4-OMeC_6H_4	**2c**	2.2/1	79
4	C_5H_{11}	2-FC_6H_4	**2d**	2.4/1	80
5	C_5H_{11}	3-FC_6H_4	**2e**	2.7/1	74
6	C_5H_{11}	4-FC_6H_4	**2f**	2.3/1	75
7	C_5H_{11}	4-$CH_3C_6H_4$	**2g**	2/1	76
8	C_5H_{11}	2-Furyl	**2h**	1.7/1	80
9	C_5H_{11}	Benzo[*d*][1,3]dioxol-6-yl	**2i**	1.1/1	60
10	C_5H_{11}	3,4-Dimethoxyphenyl	**2j**	2/1	40
11	C_5H_{11}	4-$CF_3C_6H_4$	**2k**	2.3/1	30
12	CH_2OBn	4-OMeC_6H_4	**2l**	3/1	85
13	1-Cyclohexenyl	4-OMeC_6H_4	**2m**	<5/95	59
14	C_5H_{11}	C_3H_7	**3a**	—	91
15[c]	C_5H_{11}	1-Cyclohexenyl	—	—	—

[a] For detailed experimental operation see the Supplementary data.

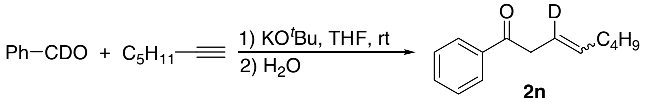
[b] Isolated yields.

[c] The reaction system was very complex and no expected product could be isolated.

electron-rich-substituted aromatic aldehydes, such as the piperonal and 3,4-dimethoxybenzaldehyde (entries 9 and 10), did not give good yields. For further investigation of this reaction, the scope of alkynes was also examined.

For example, the use of 1-((prop-2-nyloxy)methyl)benzene and 1-ethynylcyclohex-1-ene (entries 12 and 13) afforded **2l** and **2m** in a 85% and a 59% yield, respectively. Especially for entry 13, product **2m** contained a conjugated cyclohexanlidene and showed the complete *E*-form configuration (assigned by NOE analysis), which expanded the scope of this reaction in organic synthesis. The limitation to this reaction is that the reactions of an aliphatic aldehyde, such as butyraldehyde, and an α,β-unsaturated aldehyde, such as cyclohex-1-enecarbaldehyde, could not furnish the expected products (entries 14 and 15). We speculate that the acidic α-hydrogen proton of the aldehyde may complicate the reaction mixture and therefore lower the yield of the expected product.

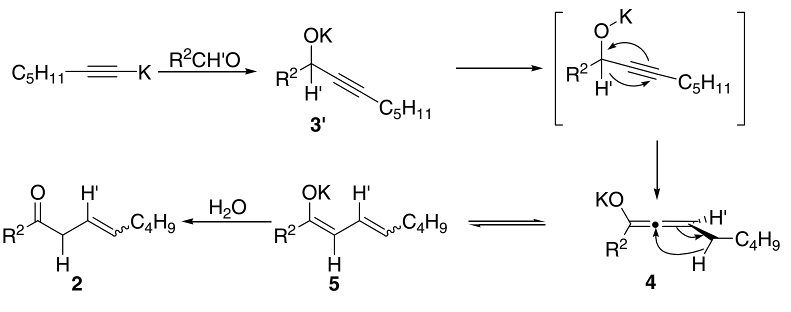
To propose a plausible reaction mechanism, we conducted the deuterium-labeling experiment. When deuterated benzaldehyde was used, the deuterium was exclusively transferred to the β-position of the carboxyl in the product **2n**, and no other deuterated product was obtained in this reaction (Scheme 2).



Scheme 2. Deuterium-labeling experiment.

Based on the observations of the above experiment and our previous research,[10] a possible mechanism that involves a double 1,3-hydride shift process was proposed (as shown in Scheme 3). Firstly, the addition of alkynyl potassium to the aldehyde $R^2CH'O$ may afford intermediate **3′**, which could form allene **4** through a 1,3-hydride shift process. Then the second 1,3-hydride shift could take place to generate thermodynamically more favorable intermediate **5**, which could be protonated to afford final product **2**.

In summary, we have developed a concise synthetic method toward β,γ-unsaturated enones in which *t*-BuOK promotes addition/isomerization reactions of



Scheme 3. Proposed reaction mechanism.

alkynes and aldehydes without a transition-metal catalyst. We believe that this method may have its extensive application in organic synthesis. Further studies on the expansion and application of this methodology are in progress and will be reported in due course.

Acknowledgments

We are grateful for the financial support of the NSFC (No. 20021001, 203900501) and Chang Jiang Scholars of Program of China.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.109.

References and notes

1. Ohtsuka, Y.; Sasahara, T.; Oishi, T. *Chem. Pharm. Bull.* **1982**, *30*, 1106, and references cited therein.
2. (a) Noda, Y.; Hashimoto, H.; Norizuki, T. *Heterocycles* **2001**, *55*, 1839; (b) Walker, R. P.; Thompson, J. E.; Faulkner, D. J. *J. Org. Chem.* **1980**, *45*, 4976; (c) Thompson, J. E.; Walker, R. P.; Wratten, S. J.; Faulkner, D. J. *Tetrahedron* **1982**, *38*, 1865; (d) Paterson, I.; Hulme, A. N. *Tetrahedron Lett.* **1990**, *31*, 7513; (e) Appendino, G.; Nano, G. M.; Viterbo, D.; Munno, G. D.; Cisero, M.; Palmisano, G.; Aragno, M. *Helv. Chim. Acta* **1991**, *74*, 495; (f) Thomas, A. F.; Thommon, W.; Willhalm, B.; Hagaman, E. W.; Wenkert, E. *Helv. Chim. Acta* **1974**, *57*, 2055.
3. Pollack, R. M.; Bounds, P. L.; Bevins, C. L. In *The Chemistry of Enones Part 1*; Patai, S., Zappoport, Z., Eds.; John Wiley & Sons: New York, 1989; p 599.
4. Kachinsky, J. L. C.; Solomon, R. G. *J. Org. Chem.* **1986**, *51*, 1393.
5. Zaidlewicz, M. *Synthesis* **1988**, 701.
6. Brown, H. C.; Soundararajan, R. *Tetrahedron Lett.* **1994**, *35*, 6963.
7. (a) Beak, P.; Berger, K. R. *J. Am. Chem. Soc.* **1980**, *102*, 3848; (b) Kang, K.-T.; Sun, U. J. *Synth. Commun.* **1994**, *24*, 1507.
8. Lu, X.; Ji, J.; Guo, C.; Shen, W. *J. Organomet. Chem.* **1992**, *428*, 259.
9. Dalpozzo, R.; Nino, A. D.; Bosco, M.; Sambri, L.; Marcantoni, E. *J. Org. Chem.* **1998**, *63*, 3745.
10. Wang, S.-H.; Tu, Y.-Q.; Chen, P.; Hu, X.-D.; Zhang, F.-M.; Wang, A.-X. *J. Org. Chem.* **2006**, *71*, 4343.
11. For recent domino coupling reactions between aldehydes and terminal alkynes, see: (a) Tejedor, D.; García-Tellado, F.; Marrero-Tellado, J. J.; de Armas, P. *Chem. Eur. J.* **2003**, *9*, 3122; (b) de Armas, P.; García-Tellado, F.; Marrero-Tellado, J. J.; Tejedor, D.; Maestro, M. A.; Gonzalez-Platas, J. *Org. Lett.* **2001**, *3*, 1905; (c) Wang, Y. G.; Cui, S. L.; Lin, X. F. *Org. Lett.* **2006**, *8*, 1241.