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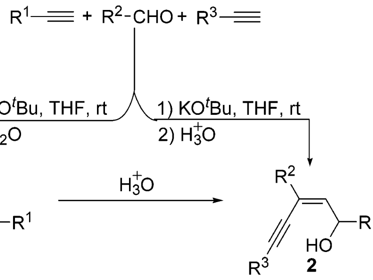
KO^{t}Bu-Promoted Three-Component Coupling of Aldehydes and Alkynes: Highly Efficient Synthesis of 1-En-4-yn-3-ols and 2-En-4-yn-1-ols

Shao-Hua Wang, Yong-Qiang Tu,* Peng Chen,
Xiang-Dong Hu, Fu-Min Zhang, and Ai-Xia Wang

*State Key Laboratory of Applied Organic Chemistry and
Department of Chemistry, Lanzhou University,
Lanzhou 730000, P. R. China*

tuyq@lzu.edu.cn

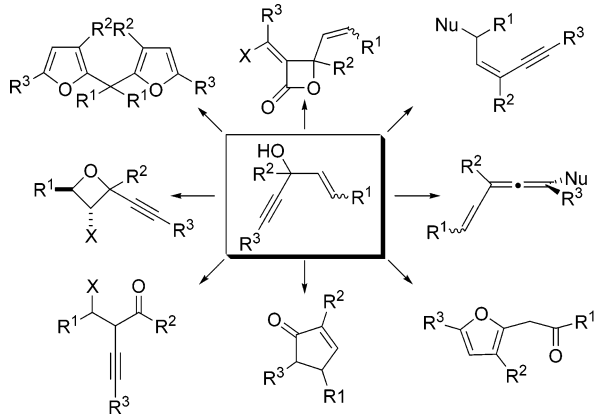
Received February 26, 2006



A KO^{t}Bu-promoted three-component coupling reaction of aldehydes and alkynes without a transition-metal catalyst was developed in which the sequential addition/isomerization/addition processes take place in one pot. This reaction could be developed into a straightforward and effective method for rapid access to stereodefined (*E*)-1-en-4-yn-3-ol and (*Z*)-2-en-4-yn-1-ol compounds.

Multifunctional molecules with double and triple bonds and hydroxyl, such as 1-en-4-yn-3-ols (Scheme 1),[1] are important key building blocks for diversity-oriented organic synthesis, and therefore, the efficient synthesis of these compounds has attracted the interest of synthetic organic chemists. As reported previously,[1a−c,h,2] however, the assembly of these groups from alkynes and aldehydes normally requires separate multistep processes, including initial preparation of propargyl alcohol, which is subsequently isomerized to the unsaturated ketone, and further addition of the resultant ketone with the alkyne. In particular, some expensive transition-metal catalysts (e.g., RhCl(PPh$_3$)$_3$ and Pd$_2$(dba)$_3$) are essential for those procedures.[3] To our knowledge, the direct three-component coupling of one aldehyde with two alkynes without transition-metal catalysts has not been reported. In connection with our research on the tandem reactions,[4] recently we found that the KO^{t}Bu/THF system could promote a three-component coupling of aldehydes and alkynes (Scheme 2), where the sequential addition/isomerization/addition processes were involved just in one pot. This strategy offered a very straightforward and efficient (rapid, economical, and high yield) method for access to (*E*)-1-en-4-yn-3-ol compounds. It is also valuable that another kind of useful compound in organic synthesis, (*Z*)-2-en-4-yn-1-ol,[5] could be produced by directly quenching the reaction mixture with excessive acid. Herein, we present our results.

SCHEME 1. Some Reactivity Patterns of 1-En-4-yn-3-ols



During studies on the preparation of structurally diverse propargyl alcohols,[6] we found that the coupling of 4-methoxybenzaldehyde with 2 equiv of phenylacetylene in the presence of KO^{t}Bu could not furnish the desired product. Unexpectedly, a multifunctional compound, the (*E*)-3-(4-methoxyphenyl)-1,5-diphenylpent-1-en-4-yn-3-ol, was isolated in 65% yield. This interesting result encouraged us to make a detailed investigation. Therefore, we examined various bases (KOH, CsOH, Bu$_4$NF, BnN(CH$_3$)$_3$OH, NaOMe, KO^{t}Bu, and Ph$_3$P) and solvents (DMF, DMSO, CH$_2$Cl$_2$, Et$_2$O, THF, toluene, and benzene). Among these tested conditions, only KO^{t}Bu could promote this reaction in CH$_2$Cl$_2$, Et$_2$O, THF, toluene, or benzene as solvent. Under general and optimized conditions (aldehyde, alkyne, and KO^{t}Bu in the mole ratios of 1:2.1:1.8 in THF, rt, quenched with H$_2$O),[7] a series of aldehydes and alkynes were tested toward this tandem coupling reaction. As indicated in Table 1, various aromatic aldehydes and alkynes were effective for this coupling reaction, and the desired products could be obtained in good to

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10.1021/jo0604078 CCC: $33.50

SCHEME 2. KO^{t}Bu-Promoted Three-Component Coupling Reaction of Aldehydes and Alkynes

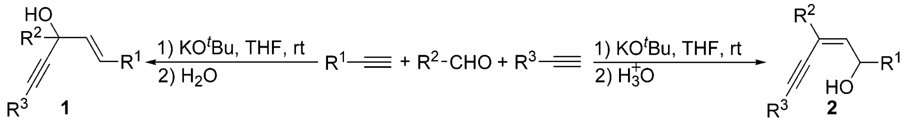
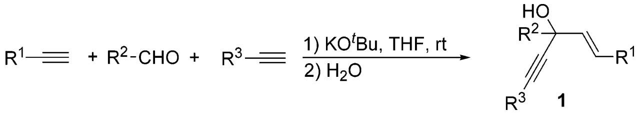


TABLE 1. Preparation of (*E*)-1-En-4-yn-3-ol 1 by KO^{t}Bu-Promoted Three-Component Coupling Reaction[a]



entry	R^1, R^2, R^3	product	time (min)	yield^b (%)
1	Ph, Ph, Ph	**1a**	2	90
2	Ph, 4-MeC$_6$H$_4$, Ph	**1b**	2	90
3	Ph, 4-N(CH$_3$)$_2$C$_6$H$_4$, Ph	**1c**	1	91
4	Ph, 2-OMeC$_6$H$_4$, Ph	**1d**	2	94
5	Ph, 3-OMeC$_6$H$_4$, Ph	**1e**	2	95
6	Ph, 4-OMeC$_6$H$_4$, Ph	**1f**	2	90
7	Ph, 2-FC$_6$H$_4$, Ph	**1g**	2	91
8	Ph, 3-FC$_6$H$_4$, Ph	**1h**	2	92
9	Ph, 4-FC$_6$H$_4$, Ph	**1i**	2	91
10	Ph, 4-CF$_3$C$_6$H$_4$, Ph	**1j**	2	93
11	Ph, 1-naphthyl, Ph	**1k**	2	90
12	Ph, 2-pyridyl, Ph	**1l**	2	81
13	Ph, 3-pyridyl, Ph	**1m**	2	80
14	Ph, 4-pyridyl, Ph	**1n**	2	85
15	Ph, 2-furyl, Ph	**1o**	2	85
16	2-CF$_3$C$_6$H$_4$, 4-OMeC$_6$H$_4$, 2-CF$_3$C$_6$H$_4$	**1p**	1	85
17	R^1, R^2, R^3 = 4-OMeC$_6$H$_4$	**1q**	2	89
18	4-FC$_6$H$_4$, 4-OMeC$_6$H$_4$, 4-FC$_6$H$_4$	**1r**	1	90
19	Ph, 1-cyclohexenyl, Ph	**1s**	1	80
20	Ph, 4-OMeC$_6$H$_4$, ^{n}amyl	**1t**	20	30
21	Ph, 4-OMeC$_6$H$_4$, 4-OMeC$_6$H$_4$	**1u**	5	89
22	Ph, 4-OMeC$_6$H$_4$, 4-FC$_6$H$_4$	**1v**	5	90
23	4-FC$_6$H$_4$, 4-OMeC$_6$H$_4$, Ph	**1w**	5	91
24	R^1 = 4-FC$_6$H$_4$, R^2 = R^3 = 4-OMeC$_6$H$_4$	**1x**	5	88
25	R^1 = R^2 = 4-OMeC$_6$H$_4$, R^3 = 4-FC$_6$H$_4$	**1y**	5	86
26	R^1, R^2 = 4-OMeC$_6$H$_4$, R^3 = Ph	**1z**	5	85

[a] All reactions were quenched with H$_2$O; for detailed experimental operation see the Supporting Information. [b] Isolated yields.

excellent yields (entries 1−18). Notably, this tandem reaction usually proceeded quickly at room temperature in most cases. An important feature of this procedure was the stereocontrolled generation of the (*E*)-alkene moiety in product **1**, which was assigned by the spectroscopic data. To expand the scope of substrates, an unsaturated cyclohex-1-enecarbaldehyde (entry 19) was further examined, and satisfyingly the final product **1s** was afforded in a good yield of 80%. When an aliphatic aldehyde such as butyraldehyde was used, however, the expected product could not be observed. Analogously, no product with the 1-en-4-yn-3-ol structure could be obtained by employing an excess of aliphatic alkyne (e.g., R^1 = R^3 = 1-heptyne) under typical reaction conditions. When both aromatic and alphatic alkynes were used, it was found that 1 equiv of phenylacetylene was first consumed in this reaction system, which was followed by the subsequent addition of 1 equiv of aliphatic 1-heptyne, and interestingly, the cross-addition product **1t** could be isolated despite of a lower yield of 30% (entry 20).[8] Based on this fact, some structurally diverse 1-en-4-yn-3-ol compounds with one single stereoisomer were readily synthesized in good yields of 85−91% by stepwise addition of two different arynes (R^1 ≠ R^3) (entries 21−26). These experimental results above suggested the presence of a possible allene intermediate with two aromatic rings (as mentioned in Scheme 4).

Interestingly, when the obtained reaction mixture was quenched with 10% H$_2$SO$_4$ aqueous solution to acidity, as tabulated in Table 2, the stereodefined (*Z*)-2-en-4-yn-1-ol **2** could be efficiently generated through a rearrangement of allylic alcohol moiety in **1**.[9] The same result (entry 6) could also be obtained by treatment of the purified **1** with excessive H$_2$SO$_4$ (10% in water) at room temperature. These experimental results have largely expanded the application scope of this reaction in organic synthesis, as the *Z*-form's 2-en-4-yn-1-ol units could be used to construct some important building blocks,[5] but their preparations required multistep transformations or transition-metal-mediated cross-coupling reactions.[5a,c,k]

To propose a possible reaction mechanism, we carried out the deuterium-labeling studies (Scheme 3). The reaction with deuterated benzaldehyde revealed that the deuterium was exclusively transferred to the γ-position of the hydroxyl in the product **3**. Performing the reaction with deuterated phenylacetylene led to 55% incorporation of deuterium at β-positin of **4**. In all labeling reaction mixtures discussed above, no other deuterated products were isolated.

These results implicated a possible mechanism as shown in Scheme 4. First, the addition of alkynyl potassium with the aldehyde R^{2}CH′O afforded the intermediate **5**, which underwent a proton exchange to form intermediate **6**. Through a 1,3-hydride

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(8) Other components were very complex and not isolated.

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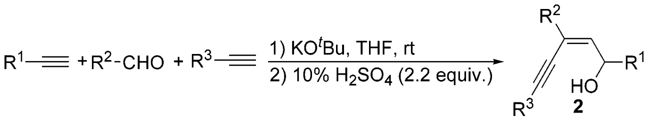
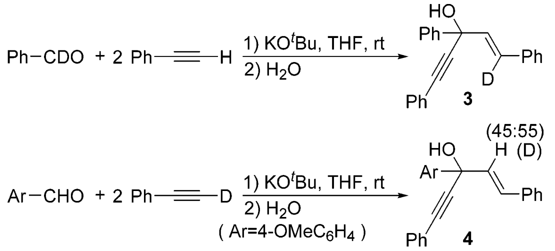
TABLE 2. Preparation of (*Z*)-2-En-4-yn-1-ol 2 through Acid-Promoted Rearrangement of 1[a]



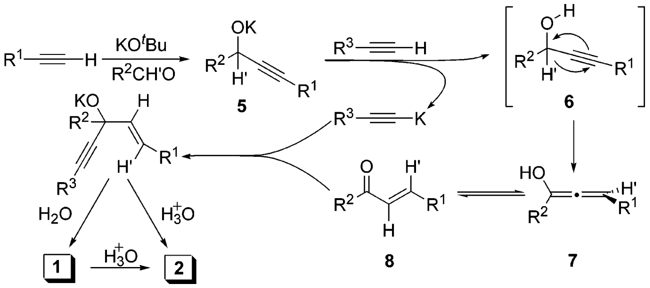
entry	R^1, R^2, R^3	product	time (min)	yield[b] (%)
1	4-FC_6H_4, 4-MeC_6H_4, 4-FC_6H_4	**2a**	2	91
2	Ph, 4-FC_6H_4, Ph	**2b**	2	86
3	Ph, 4-$OMeC_6H_4$, Ph	**2c**	2	89
4	Ph, Ph, Ph	**2d**	10	91
5	Ph, 2-$OMeC_6H_4$, Ph	**2e**	2	90
6	Ph, 4-$OMeC_6H_4$,^{n}penyl	**2f**[c]	1	90

[a] For detailed experimental operation, see the Supporting Information. [b] Isolated yields. [c] Obtained by a treatment of the purified **1t** with excessive H_2SO_4 (10% in water).

SCHEME 3. Deuterium-Labeling Studies



SCHEME 4. Plausible Reaction Mechanism



shift process of **6**, the thermodynamically more favored allene **7** was then generated.[10] After the *trans*-configured enone **8** was furnished through an allenol−enone tautomerism, the nucleophilic attack of an additional equivalent of in situ formed alkynyl potassium to **8** further gave the potassium salt of **1**. Finally, following the different quenching procedures with H_2O or H_3^+O, the final product **1** or **2** could be obtained, respectively.

In summary, we have successfully developed a novel KO^t-Bu-promoted three-component coupling reaction of aldehydes and alkynes without a transition-metal catalyst. This tandem protocol surely represents an extremely concise, practical, and economical synthesis of (*E*)-1-en-4-yn-3-ols and (*Z*)-2-en-4-yn-1-ols, which are of versatile utilities in organic synthesis. Based on the important results, the synthetic applications and the further mechanism study for this reaction are currently under active investigation.

Experimental Section

Typical Procedure 1 for Preparation of Products 1a−s. Aldehyde (0.25 mmol) was added to the mixture of alkyene (0.525 mmol) and KO^{t}Bu (0.45 mmol) in freshly distilled solvent at rt under argon atmosphere. After the reaction was stirred for the time indicated, it was cooled to 0 °C, H_2O was added to the resulting mixture, and the organic layer was separated followed by extraction of the aqueous layer with Et_2O. The combined organic extracts were washed with H_2O and brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by the column chromatography on silica gel (petroleum/ethyl acetate = 16/1) to furnish the expected product.

Typical Procedure 2 for Preparation of Products 1t−z. Aldehyde (0.25 mmol) and the second alkyne (0.25 mmol) were successively added to the mixture of the first alkyene (0.25 mmol) and KO^{t}Bu (0.45 mmol) in freshly distilled solvent at rt under argon atmosphere. After the reaction was stirred for the time indicated, it was cooled to 0 °C, H_2O was added to the resulting mixture, and the organic layer was separated followed by the extraction of the aqueous layer with Et_2O. The combined organic extracts were washed with H_2O and brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (petroleum/ethyl acetate= 16/1) to furnish the expected product.

Typical Procedure 3 for Preparation of Products 2a−f. Aldehyde (0.25 mmol) was added to the mixture of alkyene (0.525 mmol) and KO^{t}Bu (0.45 mmol) in freshly distilled solvent at rt under argon atmosphere. After the reaction was stirred for the time indicated, it was cooled to 0 °C and neutralized with H_2SO_4 (10% in water) to acidity. After the product with the *E* double bond disappeared by TLC, the organic layer was separated followed by the extraction of the aqueous layer with Et_2O. The combined organic extracts were washed with a saturated solution of $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by the column chromatography on silica gel (petroleum/ethyl acetate= 16/1) to furnish the expected product.

Acknowledgment. We are grateful for the financial support of the NSFC (Nos. 20021001 and 203900501) and the Chang Jiang Scholars Program of China.

Supporting Information Available: Spectroscopic and analytical data and copies of NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0604078

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(10) For the related reaction mechanisms studies, see: (a) Tzalis, D.; Knochel, P. *Angew. Chem.* **1999**, *111*, 1547−1549; *Angew. Chem., Int. Ed.* **1999**, *38*, 1463−1465. (b) Ishikawa, T.; Mizuta, T.; Hagiwara, K.; Aikawa, T.; Kudo, T.; Saito, S. *J. Org. Chem.* **2003**, *68*, 3702−3705. (c) Sun, M.; Shi, Q.; Huang, G.; Liang, Y.; Ma, Y. *Synthesis* **2005**, 2482−2486.