http://dx.doi.org/10.5012/bkcs.2011.32.12.4297

Solvent-free Synthesis of Propargylic Alcohols using ZnO as a New and Reusable Catalyst by Direct Addition of Alkynes to Aldehydes

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Received August 22, 2011, Accepted October 11, 2011

Under solvent-free conditions, the synthesis of propargylic alcohols by direct addition of terminal alkynes to aldehydes promoted by ZnO as a novel, commercially, and cheap catalyst is described. Furthermore, the catalyst can be reused for several times without any significant loss of its catalytic activity.

Key Words : Propargylic alcohols, ZnO, Terminal alkynes, Solvent-free conditions, Aldehydes

Introduction

Carbon-carbon bond formation reactions are amongst the important transformations in organic chemistry. The alkynylation of carbonyl compounds is a direct chain extension reaction.[1-8] Propargylic alcohols are important and versatile building blocks for many biologically active compounds and natural products such as adociacetylene B,[9] longimicin D,[10] leukotriene B_4,[11] steroid,[12] prostaglandins,[13] and carotenoids,[14] and have gained considerable attention in recent years. The most common methods to obtain propargylic alcohols are the nucleophilic addition of stoichiometric amounts of strong bases such as organolithium, dialkyl zinc or organomagnesium reagents with or without Lewis acids.[15-22] However, the use of stoichiometric amounts of metal reagents, and a separate step for metal acetylide preparation make it difficult to achieve an atom-economical process with high total efficiency. Several improved procedures including addition of alkynyl-B,[23] Al,[24,25] V,[26] and Ce[27] to carbonyl compounds represents a useful method for producing these compounds. However, these methods are not straightforward.

The in situ catalytic generation of metal acetylide and their use in addition reaction to carbonyl compounds is a good choice for this purpose. Recently, considerable progress has been developed in the alkynylation of carbonyl compounds using a Lewis acids such as $Zn(OTf)_2$, $Sn(OTf)_2$,[28-34] GaI_3,[35] $ZnCl_2$,[36] indium,[37-41] ^{i}PrMgBr,[42] $CrCl_3$[43] and Me_3Ga[44] combined with a Lewis base. Haloalkynes also form good substrates for metalation with metals such as Zn followed by the nucleophilic addition onto the carbonyl compounds.[45-48] Although the alkynylation of carbonyl compounds have advantages, but the substrate generality in many procedures are quite limited due mainly to high temperature or strongly basic conditions. Moreover, in most methods, the reaction times are long, the yields are low, the uses of strong bases are needed, and the corresponding procedures require harmful organic solvents, making them unfavorable procedures.

Despite the development of a number of Lewis acid and bases systems for the alkynylation of aldehydes, to the best of our knowledge, no attention was paid to a method for direct addition of alkynes to aldehydes without use of any active metals, solvents, and strong bases. Therefore, because of the importance of propargylic alcohols both in academic and industrial applications, it provides the constant driving force for the development of this reaction.

An important goal in modern synthetic methodology is the development of processes that are facile to carry out in the laboratory without recourse to inert atmosphere or limited using solvents especially toxic organic solvents. Therefore, the quest for cheap, environmentally friendly catalysts and mild reaction conditions is still a major challenge.

ZnO is a 'green', cheap and efficient catalyst in modern organic synthesis. It has become the focus of attention in several environmentally friendly and atom-economical organic transformations. Over the course of our continuing studies on ZnO as catalyst,[49] we herein wish to report the novel synthesis of propargylic alcohols by direct addition of terminal alkynes to aldehydes in solvent- and base-free conditions. Very simple reaction conditions and environmentally friendly catalyst make this transformation an attractive option for the straightforward preparation of propargylic alcohols.

Experimental Section

Commercial solid ZnO (SA: ~5 m^2/g) was purchased from Fluka no. 89490. ^{1}H NMR and ^{13}C NMR spectra measured on Bruker Advance DPX FT 250 and 62.9 MHz spectrometry with TMS as an internal standard. IR spectra obtained on a Perkin-Elmer or FTIR-800 instruments. Mass spectra were obtained on a Shimadzu GCMS0QP 1000EX at 20 and/or 70 eV. Elemental analyses performed on Thermo Finnigan, Flash EA 1112 series microanalyzer by the head of the CHN lab.

General Procedure. To a mixture of ZnO (0.016 g, 5 mol %) and 1-Alkyne (1 mmol), in an oil bath at 120 °C and under solvent-free conditions, aldehydes (1 mmol) were added drop-wise. Then the reaction mixture was stirred for a certain period of time as required to complete the reaction (monitored by TLC). The crude reaction mixture was extracted with EtOAc (3 × 15 mL). The organic phase were dried over $CaCl_2$ and evaporated, and the resulting crude

material was purified by column chromatography (hexan/EtOAc), which afforded the pure propargylic alcohols derivatives. All products were characterized by NMR, IR and mass spectral data which for known compounds were found to be identical with those described in the literature and only ^{1}H and ^{13}C NMR are shown and for new compounds the complete spectroscopic data are described as bellow.

Recycling of the Catalyst. Upon completion, the reaction of isobutyraldehyde **1a** with phenylacetylene **2a**, the reaction mixture was diluted with EtOAc, centrifuged and the ZnO was separated, washed with EtOAc and water, dried in an oven at 100 °C, and reused for the similar reaction. The recycling of the catalyst was repeated for four runs without appreciable loss of its catalytic activity (Table 3).

Spectral Data.

4-Methyl-1-phenylpent-1-yn-3-ol (3a):[16e] Pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.32-7.36 (m, 2H, Ar-H), 7.19-7.22 (m, 3H, Ar-H), 4.29 (d, *J* = 5.64 Hz, 1H, -C<u>H</u>(OH)-), 2.33 (br, 1H, -OH), 1.84-1.89 (m, 1H, -C<u>H</u>$(CH_3)_2$-), 0.95 (d, *J* = 6.66 Hz, 6H, -Me); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 131.6, 128.24, 128.23, 122.79, 89.0, 85.4, 68.2, 34.6, 18.2, 17.5.

1-Phenylpent-1-yn-3-ol (3b):[16e] Pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.41-7.45 (m, 2H, Ar-H), 7.28-7.32 (m, 3H, Ar-H), 4.56 (t, *J* = 6.42 Hz, 1H, -C<u>H</u>(OH)-), 2.27 (br, 1H, -OH), 1.76-1.88 (m, 2H, -CH(OH)-C<u>H</u>$_2$-), 1.08-1.04 (t, *J* = 7.32 Hz, 3H, -Me); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 131.6, 128.3, 128.2, 122.6, 90.02, 84.8, 64.1, 30.9, 9.5.

1-Phenylhex-1-yn-3-ol (3c):[22] Pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.12-7.15 (m, 2H, Ar-H), 6.98-7.06 (m, 3H, Ar-H), 4.30-4.33 (t, *J* = 6.52 Hz, 1H, -C<u>H</u>(OH)-), 2.04 (br, 1H, -OH), 1.32-1.39 (m, 2H, -C<u>H</u>$_2$-CH_2-CH_3), 1.17-1.22 (m, 2H, -CH_2-C<u>H</u>$_2$-CH_3), 0.62-0.70 (t, *J* = 6.71 Hz, 3H, -CH_2-CH_2-C<u>H</u>$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 131.6, 129.8, 128.1, 126.6, 90.40, 84.4, 63.5, 36.06,18.4, 13.9.

1-Phenylhept-1-yn-3-ol (3d): Pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.39-7.43 (m, 2H, Ar-H), 7.27-7.31 (m, 3H, Ar-H), 4.57 (t, *J* = 6.45 Hz, 1H, -C<u>H</u>(OH)-), 2.27 (br, 1H, -OH), 1.29-1.38 (m, 6H, -(C<u>H</u>$_2$)$_3$-CH_3), 0.87-0.93 (t, *J* = 5.71 Hz, 3H, -Me); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 131.6, 128.27, 128.22, 126.7, 90.3, 84.6, 64.9, 42.6, 27.7, 22.6, 14.0. EI-MS: *m/z* 188 (M^+). Anal. Calcd for molecular formula $C_{13}H_{16}O$: C, 82.94; H, 8.57%; found: C, 82.86, H, 8.48%.

4-Ethyl-1-phenyloct-1-yn-3-ol (3e): Pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.31-7.36 (m, 2H, Ar-H), 7.19-7.24 (m, 3H, Ar-H), 4.52 (t, *J* = 6.52 Hz, 1H, -C<u>H</u>(OH)), 2.25 (br, 1H, -OH), 2.19-2.23 (m, 1H, -C<u>H</u>-) 1.35-1.59 (m, 8H, -CH(C<u>H</u>$_2$-CH_3)(C_2<u>H</u>$_6$$CH_3$)), 0.82-0.90 (m, 6H, Me) ; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 131.6, 128.27, 127.5, 126.1, 121.2, 90.7, 84.7, 65.3, 45.2, 31.3 , 30.7, 21.7, 14.1, 11.8. EI-MS: *m/z* 230 (M^+). Anal. Calcd for molecular formula $C_{16}H_{22}O$: C, 83.43; H, 9.63%; found: C, 83.37, H, 9.58%.

1,3-Diphenylprop-2-yn-1-ol (3f):[16e] Pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.46-7.50 (m, 2H, Ar-H), 7.32-7.36 (m, 2H, Ar-H), 7.23-7.28 (m, 2H, Ar-H), 7.14-7.19 (m, 4H, Ar-H), 5.54 (s, 1H, -C<u>H</u>(OH)), 2.72 (br, 1H, -OH); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 140.7, 131.8, 129.9, 128.7, 128.4, 127.8, 126.8, 122.5, 88.9, 86.6, 65.0.

1-(4-Nitrophenyl)-3-phenylprop-2-yn-1-ol (3g):[14] ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.10 (d, 2H, *J* = 7.5 Hz, Ar-H); 7.64 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.36 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.25-7.30 (m, 3H, Ar-H), 5.72 (s, 1H, -C<u>H</u>(OH)), 2.56 (br s, 1H), ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 141.6, 140.4, 131.6, 128.9, 128.3, 127.3, 123.7, 121.6, 87.4, 87.5, 63.8.

1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-ol (3h):[14] ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.76 (d, 2H, *J* = 7.5 Hz, Ar-H); 7.24 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.10-7.21 (m, 5H, Ar-H), 5.52 (s, 1H, -C<u>H</u>(OH)), 2.26 (br s, 1H), ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 139.6, 133.6, 131.7, 128.8, 128.3, 128.2, 127.8, 122.7, 88.4, 86.5, 64.8.

1-(4-Methylphenyl)-3-phenylprop-2-yn-1-ol (3i):[15] ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.63 (d, 2H, *J* = 7.5 Hz, Ar-H); 7.46 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.34 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.23-7.29 (m, 3H, Ar-H), 5.51 (s, 1H, -C<u>H</u>(OH)), 2.43 (s, 3H, -Me), 2.20 (br s, 1H), ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 138.7, 137.4, 131.2, 129.6, 128.6, 128.1, 127.2, 122.4, 88.3, 86.4, 64.6, 20.8.

4-(1-Hydroxy-3-phenylprop-2-ynyl)benzonitrile (3j):[36] ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.71 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.63 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.42 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.27-7.35 (m, 3H, Ar-H), 5.64 (s, 1H, -C<u>H</u>(OH)), 2.53 (br s, 1H), ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 143.6, 136.3, 131.3, 129.5, 128.3, 127.1, 121.7, 118.5, 111.7, 87.5, 87.2, 64.0.

1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-ol (3k):[36] ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.38 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.29-7.30 (m, 3H, Ar-H), 6.89 (d, 2H, *J* = 8.0 Hz, Ar-H), 5.60 (s, 1H, -C<u>H</u>(OH)), 3.780 (s, 3H, -OMe), 2.49 (br s, 1H), ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 158.7, 133.4, 131.1, 128.7, 128.6, 128.2, 122.8, 114.1, 88.3, 86.5, 64.1, 55.2.

1-(4-Nitrophenyl)-3-phenylprop-2-yn-1-ol (3l):[35] ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.10 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.67 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.49 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.42-7.30 (m, 3H, Ar-H), 5.67 (s, 1H, -C<u>H</u>(OH)), 2.63 (br s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 147.3, 146.4, 131.2, 128.1, 127.3, 127.0, 124.7, 121.1, 87.8, 87.1, 63.4.

1-(Naphthalen-2-yl)-3-phenylprop-2-yn-1-ol (3m):[35] ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.31 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.71-7.90 (m, 3H, Ar-H), 7.37-7.46 (m, 5H, Ar-H), 7.26-7.30 (m, 3H, Ar-H), 5.33 (s, 1H, -C<u>H</u>(OH)), 2.56 (br s, 1H), ^{13}C NMR (62.9 MHz, $CDCl_3$) 134.8, 134.0, 131.2, 130.8, 129.0, 128.4, 128.3, 128.1, 125.8, 125.2, 124.7, 124.3, 123.5, 122.2, 88.6, 86.8, 63.5.

3-Phenyl-1-(pyridin-3-yl)prop-2-yn-1-ol (3n):[36] ^{1}HNMR (250 MHz, $CDCl_3$) δ 8.78 (d, 1H, *J* = 8.0 Hz, Ar-H), 8.60 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.89 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.51-7.58 (m, 2H, Ar-H), 7.34-7.40 (m, 4H, Ar-H), 5.57 (s, 1H, -C<u>H</u>(OH)), 2.53 (br s, 1H), ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 148.0, 147.4, 136.8, 134.2, 131.3, 128.2, 127.5, 123.2, 122.7, 88.4, 86.7, 62.8.

2-Methyltridec-4-yn-3-ol (3o): Pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.76-4.77 (d, *J* = 5.5 Hz, 1H, -C<u>H</u>(OH)), 2.31 (br, 1H, -OH), 1.17-1.55 (m, 15H, -C<u>H</u>$_2$-), 0.81-0.98 (m, 9H, Me); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 83.2, 80.55, 69.0, 34.5, 31.8, 29.3, 29.1, 28.5, 27.6, 22.6, 18.6, 17.6, 14.08. EI-MS: *m/z* 210 (M^+). Anal. Calcd for molecular formula $C_{14}H_{26}O$: C, 79.94; H, 12.46%; found: C, 79.82, H, 12.33%.

2-Methyl-6-(1-naphthyloxy)hex-4-yn-3-ol (3p): Pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.76 (d, *J* = 7.05 Hz, 1H, Ar-H), 8.06 (d, *J* = 6.75 Hz, 1H, Ar-H), 7.73-7.82 (m, 3H, Ar-H), 7.54-7.62 (m, 1H, Ar-H), 6.99 (d, *J* = 6.61 Hz, 1H, Ar-H), 4.85 (s, 2H, -O-C<u>H</u>$_2$-), 4.36 (d, *J* = 4.76 Hz, 1H, -C<u>H</u>(OH)), 2.92 (br, 1H, -OH), 1.85-1.88 (m, 1H, -C<u>H</u>$(CH_3)_2$), 0.97 (d, *J* = 6.5 Hz, 6H, Me); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 154.2, 135.5, 127.0, 126.4, 125.7, 124.9, 122.3, 121.08, 121.07, 109.4, 86.1, 85.6, 68.1, 56.3, 34.3, 17.6. EI-MS: *m/z* 254 (M^+); Anal. Calcd for molecular formula $C_{17}H_{18}O_2$: C, 80.28; H, 7.13%; found: C, 80.13, H, 7.04%.

2-Methyl-6-(p-tolyloxy)hex-4-yn-3-ol (3q): Pale yellow oil: IR (neat): ν 3487, 2966, 2934, 2289, 1237 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.25 (d, *J* = 7.90 Hz, 2H, Ar-H), 6.89 (d, *J* = 8.50 Hz, 2H, Ar-H), 4.68 (s, 2H, -OC<u>H</u>$_2$-), 4.11 (d, *J* = 5.42 Hz, 1H, -C<u>H</u>(OH)), 2.6 (br, 1H, -OH), 1.93 (m, *J* = 7.60 Hz, 1H, -C<u>H</u>$(CH_3)_2$), 2.21 (s, 3H, -Me), 0.83 (d, *J* = 6.60 Hz, 6H, -Me); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 155.8, 131.6, 128.3, 117.6, 90.1, 86.1, 61.9, 45.9, 33.6, 20.9, 18.5, 18.4. EI-MS: *m/z* 218 (M^+). Anal. Calcd for molecular formula $C_{14}H_{18}O_2$: C, 77.03; H, 8.31%; found: C, 76.92, H, 8.24%.

6-(4-Chlorophenoxy)-2-methylhex-4-yn-3-ol (3r): Pale yellow oil: IR (neat): ν 3452, 2935, 2875, 2298, 1245 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): 7.02 (d, *J* = 7.9 Hz, 2H, Ar-H), 6.81 (d, *J* = 7.9 Hz, 2H, Ar-H), 4.61 (s, 2H, -O-C<u>H</u>$_2$-), 4.01 (d, *J* = 6.80 Hz, 1H, -C<u>H</u>(OH)), 2.93 (br, 1H, -OH), 2.18-2.21 (m, 1H, -C<u>H</u>$(CH_3)_2$), 0.78-0.94 (m, 6H, -Me); ^{13}C NMR (62.9 MHz, DCl_3): δ 156.1, 129.6, 128.2, 116.6, 17.3, 116.2, 79.4, 79.2, 69.8, 56.3, 34.3, 17.6; EI-MS: *m/z* 238 (M^+). Anal. Calcd for molecular formula $C_{13}H_{15}ClO_2$: C, 65.41; H, 6.33%; found: C, 65.36, H, 6.24%.

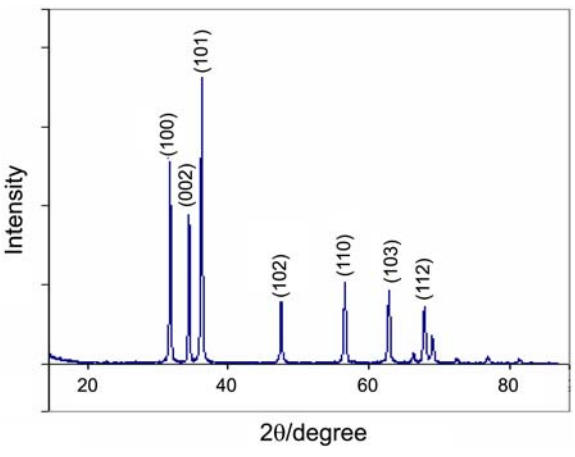


Figure 1. The XRD patterns of ZnO.

1-(4-Chlorophenoxy)-4-(naphthalen-2-yloxy)but-2-yn-1-ol (3s): Yellow solid: mp. > 300 °C. ^{1}H NMR (250 MHz, $CDCl_3$): 8.12 (d, *J* = 7.15 Hz, 1H, Ar-H), 7.89 (d, *J* = 7.18 Hz, 1H, Ar-H), 6.89-7.51 (m, 6H, Ar-H), 6.71 (d, *J* = 7.20 Hz, Ar-H), 4.56 (s, 2H, -O-C<u>H</u>$_2$-), 4.20 (s, 1H, -C<u>H</u>(OH)), 2.84 (br,1H, -OH); ^{13}C NMR (62.9 MHz, DCl_3): δ 156.2, 139.5, 135.4, 133.6, 131.6, 128.9, 128.4, 127.1, 126.3, 124.7, 122.1, 121.1, 121.05, 109.5, 86.1, 85.5, 68.2, 56.2; EI-MS: *m/z* 322 (M^+). Anal. Calcd for molecular formula $C_{20}H_{15}ClO_2$: C, 74.42; H, 4.68%; found: C, 74.35, H, 4.55%.

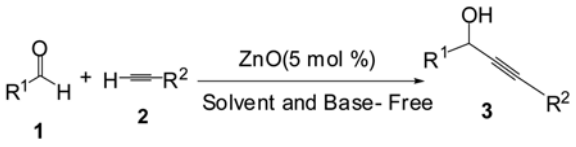
Results and Discussion

Initially, the solid ZnO (Fluka no. 89490), which was used in this reaction was characterized by X-ray diffraction

Table 1. Optimization of the synthesis of 1,3-diphenylprop-2-yn-1-ol **3a** using ZnO[a]

Entry	Phenyl acetylene **2a** (equiv)	Catalyst (mol%)	Solvent[b]	Base[c]	Time (h)	Yield (%)[d]
1	1	ZnO (5)	none	none	24	50
2	1.5	ZnO (5)	none	none	24	50
3	2	ZnO (5)	none	none	7	98
4	2.5	ZnO (5)	none	none	7	98
5	1	ZnO (5)	none	none	7.5	98[e]
6	1	ZnO (5)	MeOH	none	24	trace[e]
7	1	ZnO (5)	THF	none	24	trace[e]
8	1	ZnO (5)	DMF	none	24	trace[e]
9	1	ZnO (5)	CH_3CN	none	24	trace[e]
10	1	ZnO (5)	PEG-300	none	24	trace[e]
11	1	ZnO (5)	CH_2Cl_2	none	24	trace[e]
12	1	ZnO (5)	Toluene	none	24	trace[e]
13	1	ZnO (5)	none	K_2CO_3	12	trace[e]
14	1	ZnO (5)	none	Na_2CO_3	12	trace[e]
15	1	ZnO (5)	none	K_3PO_4	24	trace[e]
16	1	ZnO (5)	none	Cs_2CO_3	24	trace[e]
17	1	ZnO (5)	none	Et_3N	12	trace[e]
18	1	ZnO (5)	Toluene	Et_3N	24	trace[e]
19	1	ZnO (5)	CH_2Cl_2	Et_3N	24	trace[e]
20	1	none	none	none	24	0[e]
21	1	ZnO (20)	none	none	7	98[e]
22	1	ZnO (15)	none	none	7	98[e]
23	1	ZnO (10)	none	none	7	98[e]
24	1	ZnO (5)	none	none	7.5	98[e]
25	1	ZnO(4)	none	none	10	90[e]
26	1	ZnO (2)	none	none	24	85[e]
27	1	MgO (5)	none	none	24	0[e]
28	1	SiO_2 (5)	none	none	24	0[e]
29	1	Al_2O_3 (5)	none	none	24	0[e]
30	1	K_2CO_3 (5)	none	none	24	0[e]
31	1	CaO (5)	none	none	10	0[e]
32	1	TiO_2(5)	none	none	24	0[e]

[a]Conditions: Isobutyraldehyde (1 mmol), in an oil bath at 120 °C. [b]2 mL of the appropriate solvents were used under reflux conditions. [c]1 mmol of the appropriate bases were used. [d]Yields were determined by GC. [e]Isobutyraldehyde (1 mmol) was added drop wise.



Scheme 1. Synthesis of propargylic alcohol derivatives catalyzed by ZnO under solvent-free condition.

technique. XRD pattern of solid ZnO is shown in Figure 1. The observed diffraction peaks in the recorded XRD patterns are in agreement with those of the JCPDS card 89-7102 for hexagonal ZnO and could be indexed to the hexagonal Wurtzite structure. No peaks of any other phase were detected. From the FWHM of diffraction lines, crystallite size is estimated employing *Scherrer's* formula. Average size is > 1 mm.

In the next step, the commercially available solid ZnO (5 mol %) was mixed with benzaldehyde **1a** (1 equiv) and phenylacetylene **2a** (1 equiv) at 120 °C under solvent- and base-free conditions and 24 hour later, 1,3-diphenylprop-2-yn-1-ol **3a** was isolated in 50% yield (Scheme 1, Table 1). When the amount of phenylacetylene was increased to two equivalents, the yield of the product was promoted to 98% and the reaction time decreased to 7 hours (entry 3). When the amount of phenylacetylene was less than 2 equiv, a competitive aldol condensation by-product was observed. Insteade of using excess amount of phenylacetylene, one simple way is the dropwise addition of aldehyde to alkyne.

Table 2. Synthesis of propargylic alcohols catalyzed by ZnO[a]

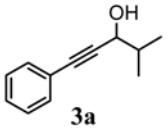
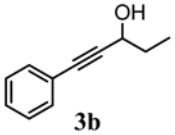
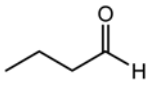
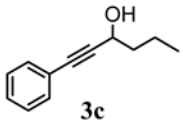
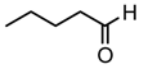
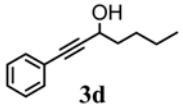
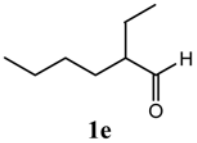
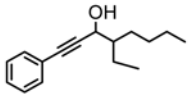
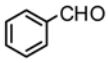
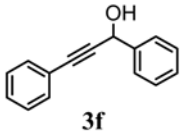
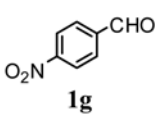
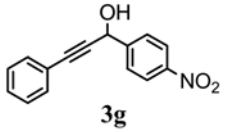
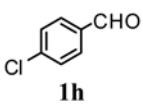
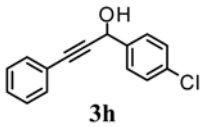
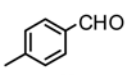
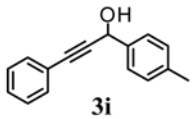
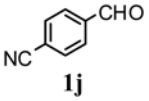
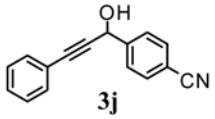
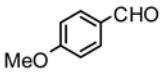
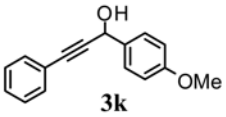
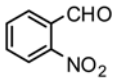
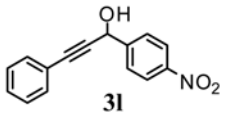
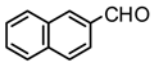
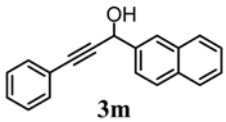
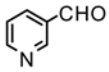
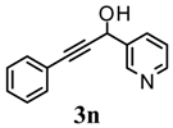
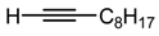
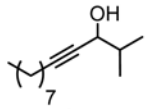
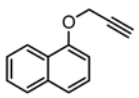
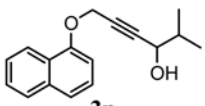
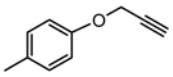
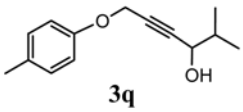
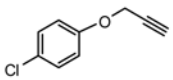
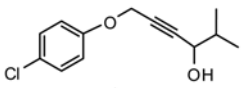
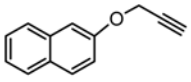
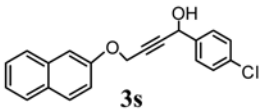
Entry	Aldehyde	Alkyne	Product	Time (h)	Yields[b] (%)
1	 **1a**	 **2a**	 **3a**	7	98
2	 **1b**	**2a**	 **3b**	5	98
3	 **1c**	**2a**	 **3c**	9	95
4	 **1d**	**2a**	 **3d**	10	95
5	 **1e**	**2a**	 **3e**	15	70
6	 **1f**	**2a**	 **3f**	7	98
7	 **1g**	**2a**	 **3g**	7	90
8	 **1h**	**2a**	 **3h**	7	90
9	 **1i**	**2a**	 **3i**	12	70

Table 2. Continued

Entry	Aldehyde	Alkyne	Product	Time (h)	Yields[b] (%)
10	 **1j**	**2a**	 **3j**	7	92
11		**2a**	 **3k**	12	75
12		**2a**	 **3l**	7	95
13		**2a**	 **3m**	12	85
14		**2a**	 **3n**	7	90
15	**1a**	 **2b**	 **3o**	12	70
16	**1a**	 **2c**	 **3p**	11	65
17	**1a**	 **2d**	 **3q**	13	60
18	**1a**	 **2e**	 **3r**	12	60
19	**1h**	 **2f**	 **3s**	14	65

[a]Conditions: aldehyde (1 mmol), alkyne (1 mmol), and ZnO (5 mol %), in an oil bath at 120 °C. [b]Yields are determined by GC.

According to Table 1, entry 5, when iso-butyraldehyde was added in small portion to the phenylacetylene, the corresponding product was obtained in 98% yield after 7.5 h. So to avoid aldol reactions, instead of reduplication of the phenylacetylene, slow addition of aldyhyde to alkyne was performed.

To obtain the optimized reaction conditions, several bases (1 equiv) and solvents (2 mL under reflux temperature) have been examined (Table 1, entries 6-19). This catalyst was not efficient in the presence of organic solvents such as methanol, acetonitrile, toluene, and strong bases such as K_2CO_3, K_3PO_4, Cs_2CO_3, and Na_2CO_3. Probably, ZnO surface contributes to the reaction so the solvents and bases may deactivate the catalyst and may also act as a contaminant, so it caused to decrease the reaction yields. Control experiment did not afford any products in the absence of ZnO even after 48 h (entry 20).

The quantitative variation of ZnO had performed influence

on the reaction progress. The best amounts of nano ZnO were 20, 15, 10, and 5 mol %, which afforded the desired product in 98% yields (entries 21-24). However, when the amount of ZnO decreased, the yield of the product was also decreased but the reaction time increased (entries 25, 26). So, less than 5 mol %, ZnO was not an effective catalysis.

The yield of compound **3a** has been examined by other organic catalysts (entries 27-32). We encountered with ineffective reactions, when MgO, SiO_2, Al_2O_3, K_2CO_3, CaO, and TiO_2 were used under the same conditions. Therefore, the optimum reaction condition was found to be the dropwise addition of 1 mmol aldehyde into 1 mmol alkyne in the presence of ZnO (5 mol %) under solvent-free and without any additional bases. The experimental procedure is simple and straightforward.

With the above optimized conditions in hand, varieties of aromatic and aliphatic aldehydes with various terminal alkynes were screened to evaluate the scope of this reaction. We were pleased to find that all substrates were smoothly converted to the corresponding propargylic alcohols in good to excellent yields. The results are listed in Table 2.

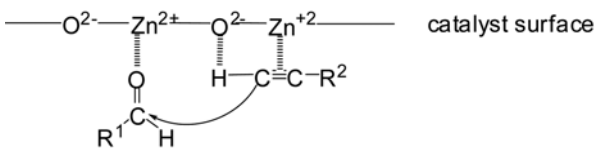
Aliphatic aldehydes showed high reactivity and afforded the corresponding propargylic alcohols in excellent yields. Both linear and branched aliphatic aldehydes (entries 1-5) undergo alkynylation with phenylacetylene in excellent yields. It is interesting to note that easily enolizable aldehydes (alkyl aldehydes C_3-C_5) produced alkynylated products **3a-e** with 95-98% yields and no aldol condensation by products were formed. Benzaldehyde derivatives having both electron-donating and withdrawing substituents, 2-naphthaldehyde, and a heterocyclic aldehyde gave the products in good to excellent yields (entries 6-14).

We also checked on the reaction of aliphatic-substituted acetylenes such as 1-octyne, and alkynes **2b-e** with isobutyraldehyde under optimized conditions. Alkylacetylenes have low reactivity than aromatic acetylenes and many other catalysts or reagents reported previously did not work with these alkynes to produce propargylic alcohols.[38] As it is shown in Table 2, entries 15-18, less reactive alkylacetylenes (much less acidic than **2a**) were also applicable to the alkynylation of an aldehydes in good yields. In particular, alkynes **2b-e** underwent the addition reaction with isobutyraldehyde **1a** to furnish the corresponding propargylic alcohols in 60-65% yields (entries 16-18), which is a cost-effective process for the preparation of new compounds. As

Table 3. Reusability of ZnO in the synthesis of **3a**[a]

Number of use	Used ZnO (g)	Recovered ZnO % (g)	Yield of **3a** %[b]
Fresh	0.08	98 (0.078)	98
1	0.078	98 (0.076)	98
2	0.076	98 (0.075)	98
3	0.076	95 (0.072)	92
4	0.072	95 (0.067)	90

[a]Conditions: isobutyraldehyde (5 mmol), phenylaceylene (10 mmol), in an oil bath at 120 °C. [b]Isolated yields.



Scheme 2. Proposed mechanism for alkynylation *via* dual activation of both carbonyl and alkynes with ZnO as catalyst.

indicated above, solvent or base totally interrupted this alkynylation reaction, in this case to show the ability of ZnO as a good catalyst we apply this method to a solid alkyne and aldyhydes. As shown in Table 2 (entry 19) addition of 4-chlorobenzaldehyde with alkyne **2f** afforded the corresponding alkynylated product **3s** in good yield. These substrates were melted under 120 °C.

In order to investigate the recovery and reuse of the catalyst to improve that the process is heterogeneous, after the reaction was completed, the mixture was dilute with EtOAc and ZnO was removed by filtration. The catalyst after drying in an oven at 100 °C was reused for the same reaction. As shown in Table 3, the yields of **3a** only decrease a little after the reuse of ZnO for four times.

Although the mechanism of ZnO catalyzed alkynylation of aldehydes has not yet been clarified, a mechanistic proposal for the role of ZnO as the catalyst is shown in Scheme 2. ZnO has Lewis acidic (Zn^{2+}) and basic sites (O^{2-}) and therefore could have dual activation. The oxygen of the carbonyl group is coordinated to Zn^{2+}, resulting in the increased reactivity of aldehyde. The Lewis basic sites of ZnO (O^{2-}) is coordinated to the hydrogen of terminal alkynes and followed by the nucleophilic attack to the carbonyl carbon of the aldehyde (Scheme 2).

Conclusions

In conclusion, we developed an efficient, new catalytic alkynylation of aldehydes using ZnO in solvent- and base-free conditions. The present method is complementary to the previously reported methods, and applicable to various aromatic and aliphatic aldehydes and alkynes. The cheap catalyst is commercially available and works well under solvent and base free conditions. The identity of the synthesis of propargyl chiral molecules and reaction mechanism remains obscure, and further work in this area is underway in our laboratory.

Acknowledgments. I gratefully acknowledge the support of this work by the Shiraz University Research Council.

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