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Zinc-mediated alkynylation of carbonyl compounds with iodoalkynes: a facile synthesis of propargyl alcohols

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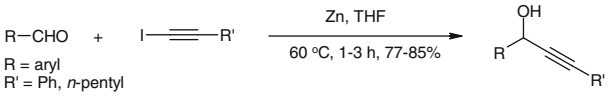
ABSTRACT

A straightforward synthesis of propargyl alcohols from alkynyl iodides and carbonyl compounds using zinc is described.

C–C bond formation reaction is a very important transformation in organic chemistry. Toward this direction, addition of alkynyl halides to carbonyl compounds is a direct chain extension reaction.[1] Also, the resulting propargyl alcohol is an excellent handle for further manipulation. They are versatile substrates for the synthesis of pharmacologically relevant molecules.[2] Recently, there has been much focus on propargyl alcohols, specifically aryl propargyl alcohols. Our own interest on Lewis acid catalyzed reactions has initiated several projects in which iodine,[3] $NbCl_5$,[4] and PMA-SiO_2[5] have been utilized for the substitution reactions on benzylic and aryl propargylic alcohols. Although there are several methods[6] available for the preparation of propargyl alcohols using metalated alkynes in the presence of various Lewis acids[7] or dialkylzinc[8] reagents, many of these reactions are sensitive and low temperatures are needed to stabilize the metal acetylides. Halo alkynes also form good substrates for metalation with magnesium[9] or in Barbier-type reaction, for example, using SmI_2.[10] The use of indium[11] or Ti(OiPr)$_4$, ^{i}PrMgBr,[12] chromium chloride,[13] and Me_3Ga[14] for metalation followed by the nucleophilic addition onto the carbonyl compound has been described. New protocols for this transformation are always welcome due to the importance of propargyl alcohols.

While working on substitution reactions of aryl propargylic alcohols, we investigated a simple procedure for the preparation of aryl propargyl alcohols. We reasoned that zinc[15] could serve as a reagent for the carbonyl alkynylation. Initially, we treated an alkynyl iodide with benzaldehyde in the presence of zinc dust (1 equiv) in THF at room temperature and found that by heating the reaction mixture to reflux for 2 h, the starting material was completely consumed and a new spot developed (TLC). This product was isolated and characterized as the corresponding aryl propargylic alcohol (Scheme 1).



Scheme 1.

With the success of this reaction, we studied the scope and generality of this transformation. Different solvents such as CH_3CN, DMSO, DMF, DCM, Et_2O, and THF were investigated, and we found that THF and Et_2O were the best in terms of yield. The reaction did not proceed in CH_3CN, DMSO or DMF and the starting materials were recovered even after heating the solution to 80 °C for 6 h. Also, increasing the amount of zinc did not change the yield significantly. However, decreasing the quantity of zinc led to decreased yields and increased reaction times. Thus, one equivalent of zinc was necessary to obtain optimum yields in this transformation.

Various substituted aromatic aldehydes were subjected to this protocol,[16] and we found that all the reactions worked well and yielded the expected products[17] in good yields (see Table 1). Surprisingly, nitrogen-containing substrates such as 2-nitro benzaldehyde, 4-nitrobenzaldehyde, and *N*-Boc-proline-carboxaldehyde did not undergo this transformation, and the starting material was recovered in all the cases.

With the successful results obtained from aldehydes, we attempted a similar transformation with ketones. We were pleased to note that the reaction worked well with cyclohexanone.[18] Mechanistically, we believe that zinc inserts into the iodoalkyne and then participates in nucleophilic addition to the carbonyl compound (see Scheme 2).

In conclusion, a simple protocol for the preparation of propargylic alcohols starting from alkynyl iodides and carbonyl compounds mediated by zinc has been described. Readily available zinc, clean

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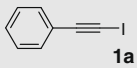
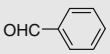
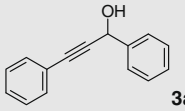
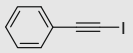
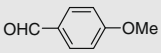
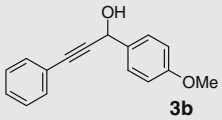
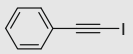
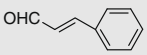
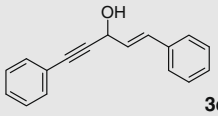
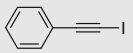
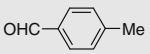
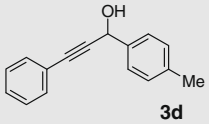
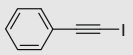
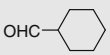
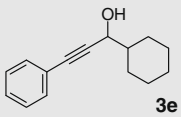
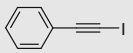
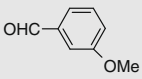
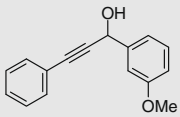
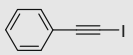
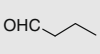
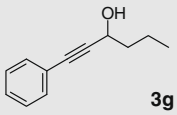
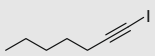
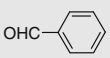
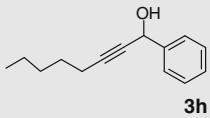
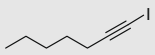
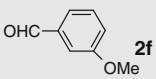
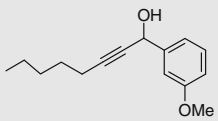
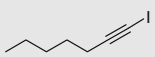
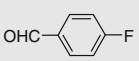
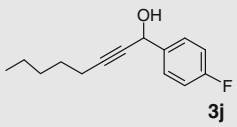
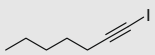
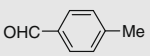
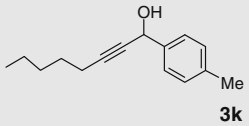
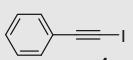
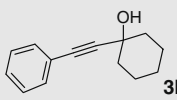
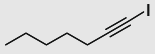
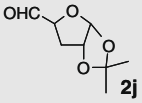
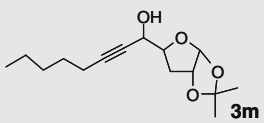
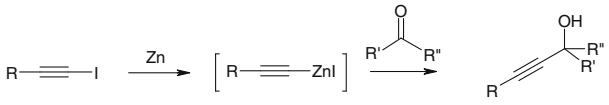
Table 1
Zinc-mediated addition of iodocetylenes to carbonyl compounds

Entry	Iodoacetylene	Carbonyl compounds	Product[a]	Time (h)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	1.0	85
2	 **1a**	 **2b**	 **3b**	1.5	80
3	 **1a**	 **2c**	 **3c**	1.0	77
4	 **1a**	 **2d**	 **3d**	2.0	82
5	 **1a**	 **2e**	 **3e**	2.0	80
6	 **1a**	 **2f**	 **3f**	1.5	78
7	 **1a**	 **2g**	 **3g**	2.0	80
8	 **1b**	 **2a**	 **3h**	1.0	78
9	 **1b**	 **2f**	 **3i**	2.0	85
10	 **1b**	 **2h**	 **3j**	2.0	82
11	 **1b**	 **2d**	 **3k**	2.0	81
12	 **1a**	 **2i**	 **3l**	3.0	80
13	 **1b**	 **2j**	 **3m**	2.0	50

[a] Product were characterized by IR, ^{1}H, $^{13}CNMR$ and mass spectroscopy.
[b] Isolated yields after column chromatography.



Scheme 2. Proposed mechanism for the alkynylation of carbonyl compounds.

reaction conditions and an easy workup procedure make this an attractive protocol for the synthesis of various aryl propargylic alcohols.

Acknowledgments

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16. *Typical experimental procedure*: To a solution of aldehyde (1 mmol) and iodoacetylene (1 mmol) in THF (3 mL) was added zinc dust (1 mmol), and the mixture was refluxed for completion of the reaction (TLC). The reaction mixture was cooled and filtered, and the filtrate was washed with saturated aq NH_4Cl solution. The organic layer was concentrated and the residue was purified by column chromatography (ethyl acetate/hexane) to yield the pure product.
17. *Spectroscopic data of a few representative examples*: *1,3- Diphenyl-prop-2-yn-ol* (**3a**): Yellow liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.29 (s, 1H), 5.62 (s, 1H), 7.26–7.46 (m, 8 H), 7.54–7.59 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 65.02, 86.60, 88.67, 122.34, 126.69, 128.25, 128.37, 128.54, 128.61, 131.70, 140.56. IR (thin film): 757, 1026, 1449, 1489, 1629, 2854, 2924, 3425 cm^{-1}. ESIMS: *m*/*z* 231 (M^++Na). HRMS calcd for $C_{15}H_{12}ONa$, 231.0785: found 231.0779. *1,5-Diphenyl-pent-1-en-4-yn-3-ol* (**3c**): Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): 1.94 (d, *J* = 5.2 Hz, 1H), 5.22 (t , *J* = 4.5 Hz, 1H), 6.34 (dd, *J* = 6.0, 15.8 Hz, 1H), 6.80 (d, *J* = 15.8 Hz, 1H), 7.20–7.33 (m, 6H), 7.39–7.46 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.64, 86.65, 88.15, 122.57, 123.56, 127.03, 128.25, 128.32, 128.42, 128.98, 132.22, 123.51, 136.28. IR (thin film): 691, 756, 963, 1489, 2924, 3396 cm^{-1}. ESIMS: *m*/*z* 257 (M^++Na). HRMS calcd for $C_{17}H_{14}ONa$,257.0942: found 257.0943. *1-Cyclohexyl-3-phenyl-prop-2-yn-1-ol* (**3e**): Light yellow liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08–1.33 (m, 5H), 1.63–1.94 (m, 7H), 4.31, (t, *J* = 5.8 Hz, 1H), 7.25–7.30 (m, 3H), 7.37–7.41 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.59, 25.82, 28.58, 44.21, 67.47, 85.45, 89.31, 122.74, 128.12, 128.2, 131.57. IR (thin film): 756, 1026, 1447, 2853, 2926, 3387 cm^{-1}. ESIMS: *m*/*z* 214 (M^+). HRMS calcd for $C_{15}H_{18}ONa$, 237.1255: found 237.1250.
18. Acetophenone and benzophenone did not respond to the present protocol.