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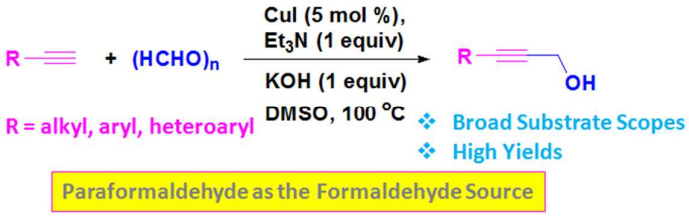

Synthesis of primary propargylic alcohols from terminal alkyne and paraformaldehyde catalyzed by Copper(I) Iodide, without using any moisture sensitive reagents.

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ARTICLE TYPE

Copper(I) Iodide Catalyzed Synthesis of Primary Propargylic Alcohols from Terminal Alkyne

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A highly efficient and practical method for the synthesis of primary propargylic alcohols has been developed using CuI as catalyst and paraformaldehyde as the formaldehyde source. The reaction was performed under mild reaction conditions offering the desired products in good to excellent yields with variety of terminal alkynes.

Alkynylation of aldehydes is one of the most important reactions widely used in organic synthesis which lead to the production of propargylic alcohols.[1] Among the various aldehydes, alkynylation of formaldehyde has drawn significant attention as it forms primary propargylic alcohols. These primary alcohols have a wide range of applicability. They are useful building blocks in all types of organic synthesis, particularly for that of different heterocyclic scaffolds[2] (Fig 1) and complex compounds[3] (Fig 2).

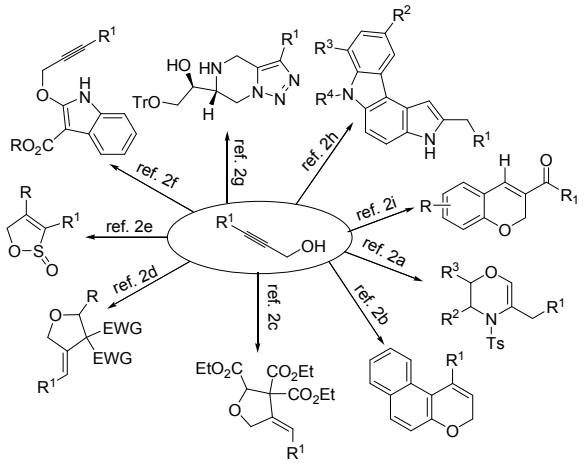


Figure 1. Synthesis of heterocyclic scaffolds.

There are several methods in literature for synthesis of secondary and tertiary propargylic alcohols from terminal alkynes[4] but synthesis of primary propargylic alcohols from the alkyne and formaldehyde is still a challenge because formaldehyde is not easily accessible from the polymeric forms. Primary propargylic alcohols are usually synthesized by reaction of phenyl acetylene and formaldehyde. Literature survey has yielded three general methods of synthesis: (i) passing of gaseous formaldehyde which is generated by the thermal depolymerisation of paraformaldehyde[5] or 1,3,5-trioxane[6] over the alkynyl Grignard reagent by a current of dry nitrogen, (ii) the reaction of ethereal solution or suspension of lithium acetylide with in situ generated formaldehyde from dry paraformaldehyde[7] and (iii) reaction of alkynyl Grignard reagents with the *in situ* generated formaldehyde from its linear polymer.[8] All of these methods require low temperature, moisture sensitive reagents and strong base thus making the procedures operationally complex and economically restrictive.

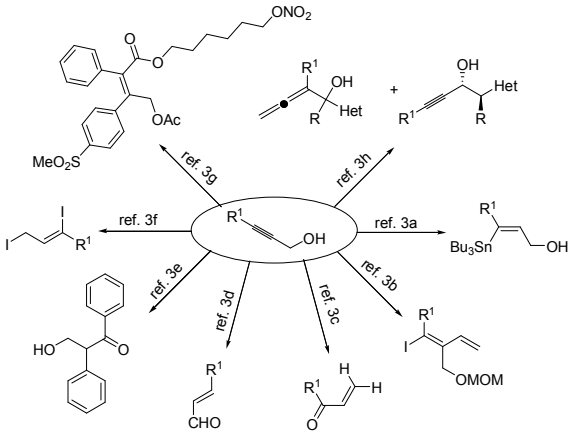


Figure 2. Synthesis of complex compounds.

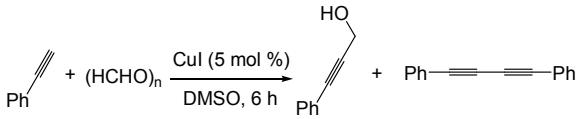
The limitations of the general methods prompted us to search and develop an alternative method to construct primary propargylic alcohols from terminal alkynes.

During preliminary investigations, reaction between phenyl acetylene and paraformaldehyde was examined as model system using different reaction conditions (Table 1, 2 and 3). In all the reactions Cu-salts were used as catalysts since they are known to play a vital catalytic role in modern organic synthesis.[9] Among the Cu-salts, CuI in particular reacts with terminal alkynes to form copper acetylynic complex[10] which acts as a good nucleophile. The use of CuI as catalyst in our synthesis of primary propargylic alcohols was dron from the work of M. Shibasaki and his group,[11] where Cu-catalyst has been used in the form of Cu(I)Alkoxide for alkynylation of trifluoromethyl

ketones to form CF_3-substituted tertiary propargyl alcohol. Initially, we were interested about the possibility of Cu-based catalysts for transformation of formaldehyde and terminal alkyne to prepare primary propargylic alcohols since the mechanism of both the reaction should be similar.

At first, the reaction was performed in presence of CuI and triethyl amine without potassium hydroxide, where 71% of homocoupling product (Table 1, entry 1) was isolated. However, introduction of potassium hydroxide gave our desired product, primary propargylic alcohols in good yield (Table 1, entry 2). As the amount of potassium hydroxide was increased, the yield of propargylic alcohols increased with decrease of the homocoupling products. Preliminary screening of the reaction conditions prompted us to select CuI (5 mol %) as catalyst, and KOH (1 equiv.) as the base. We examined different organic bases such as triethyl amine, pyridine and triphenyl phosphine in the reaction. Among these, triethyl amine is more environmentally friendly and also proved better than others in terms of yield of the desired products.

Table 1. Screening of bases in reaction conditions



1 **2** **3a** **4a**

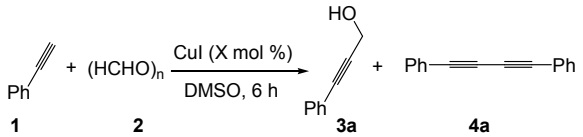
Entry[a]	Organic base	Inorganic base	Yields[b] (%) **3a**	Yields[b] (%) **4a**
1	Et_3N	--	--	71
2	Et_3N	KOH	86	--
3	Pyridine	--	--	81
4	PPh_3	--	--	56
5	DMAP	--	--	61
6	Pyridine	KOH	75	--
7	Pyridine	NaOH	59	--
8	Pyridine	K_2CO_3	31	26
9	Et_3N	NaOH	79	--
10	--	NaOH	--	--[c]

[a] Reaction Conditions: 0.5 mmol of **1**, 1 mmol of **2**, 2 mL DMSO, organic base 0.5 mmol, inorganic bases 0.5 mmol, 100 ºC (oil bath). [b] isolated yields after chromatography on silica gel. [c] Yellowish suspension.

The reaction in absence of triethylamine did not proceed (entry 10, table 1). Thus, preliminary observations (Table 1) have shown that both KOH and Et_3N were essential for this transformation. Next our goal was to search for optimum temperature and the proper ratio of KOH and Et_3N to obtain primary propargylic alcohol as the sole product.

Results presented in Table 2, showed 100 ºC as the optimum temperature and 1:1 ratio of KOH and Et_3N with respect to phenyl acetylene was the best conditions for this transformation (Table 2, entry 5).

Table 2. Optimization of the reaction temperature and ratios of bases



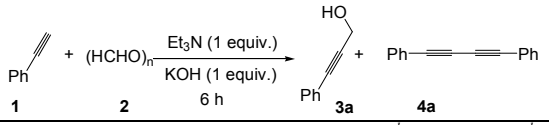
1 **2** **3a** **4a**

Entry[a]	Catalyst loading (mol%)	Et_3N (equiv.)	Temp (°C)	KOH (equiv.)	Yields[b] (%) **3a**	Yields[b] (%) **4a**
1	5	0.1	100	1	22	12
2	5	0.5	100	1	25	5
3	5	1	100	0.1	6	70
4	5	1	100	0.5	46	26
5	5	1	100	1	86	--
6	10	1	100	1	79	--
7	15	1	100	1	77	--
8	10	1	120	1	62	--
9	10	1	80	1	57	--

[a] Reaction Conditions: 0.5 mmol of **1**, 1 mmol of **2**, 2 mL DMSO. [b] Isolated yields after chromatography on silica gel.

Subsequently, we directed our attention in choosing a suitable solvent and in examining the effect of other copper salts as catalyst for the above transformation. We have experimented with some high boiling solvents like DMSO, DMF, 1,2-DCE etc. and CuI, CuBr, Cu(OAc)2 as catalysts. To examine the role of other metal salt we have performed the same experiment using DMSO as solvent and NiI_2, ZnI_2, $FeCl_3$ and $CoCl_3$ as catalyst (entry 7-10) and isolated very low yield. But only CuI as catalyst in DMSO solvent yielded the desired product primary propargylic alcohols without any byproducts. In all other cases it was observed that homocoupling products were major or sole products.

Table 3. Optimization of solvent and catalyst

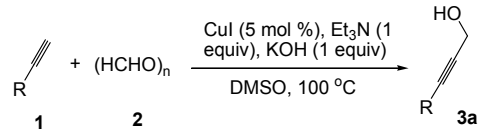


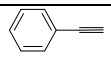
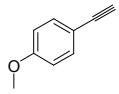
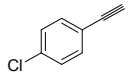
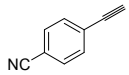
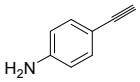
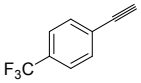
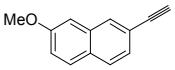
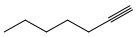
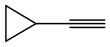
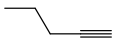
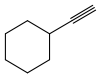
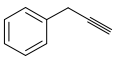
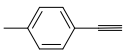
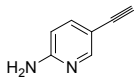
Entry[a]	Solvent	Catalyst	Yields[b] (%) 3a	Yields[b] (%) 4a
1	DMF	CuI	55	40
2	1,2-DCE	CuI	7	75
3	1,4-Dioxane	CuI	<5	79
4	DMSO	CuI	91	--
5	DMSO	CuBr	20	70
6	DMSO	$Cu(OAc)_2$	--	82
7	DMSO	$NiCl_2$	25	46
8	DMSO	ZnI_2	15	35
9	DMSO	$FeCl_3$	15	22
10	DMSO	$CoCl_3$	20	56

[a] Reaction Conditions: 0.5 mmol of **1**, 1 mmol of **2**, 2 Ml solvent, Et_3N 0.5 mmol, KOH 0.5 mmol, catalyst 5 mol%, 100 °C (oil bath). [b] Isolated yields after chromatography on silica gel.

After optimizing the reaction conditions, transformation was examined with a variety of terminal alkyne systems. Phenyl acetylene and its different derivatives were found to react satisfactorily to give the corresponding primary propargylic alcohols in good yields. Furthermore electron-releasing (Table 4, entries 2 & 5) and electron-withdrawing substituent (Table 4, entry 6) on the phenyl ring were almost equally effective during the transformation with good to excellent yields. Moreover, this method was not only effective for simple aliphatic terminal alkyne with yields ranging from 74 % to 84 % (Table4, entry 9-13) but also alkyne with highly strained cyclopropane ring (Table 4, entry 10). Unfortunately, it was found that the compounds like 4-ethynylbenzonitrile and 2-ethynylpyridine (Table 4, entries 4 & 8) fails to react in the following transformations. An important advantage of this method is that the primary amine group remains unchanged which has been substantiated by deuterium exchange experiment. To explore the reaction for other aldehyde, we have examined benzaldehyde and butyraldehyde but no expected product was observed.

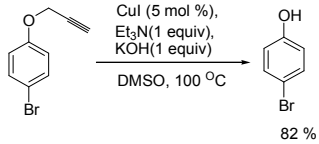
Table 4. Substrates Scope of the Reaction.



Entry[a]	Substrates	Products	Time (h)	Yields[b]
1		**3a**	4	91
2		**3b**	8	77
3		**3c**	7	75
4		**3d**	8	00[c]
5		**3e**	5	77
6		**3f**	4	86
7		**3g**	4	85
8		**3h**	5	00[c]
9		**3i**	5	78
10		**3j**	5	85
11		**3k**	5	74
12		**3l**	5	80
13		**3m**	5	84
14		**3n**	5	84
15		**3o**	4	82
16		**3p**	8	45

[a] Reaction Conditions: 1 mmol of **1**, 2 mmol of **2**, 3 mL DMSO, Et_3N 1 mmol, KOH 1 mmol, CuI 5 mol%, 100 °C (oil bath). [b] Isolated yields after chromatography on silica gel. [c] Starting material isolated.

In this context it is worthy to mention that when propargylic ether underwent the reaction, depropargylation of propargylic ether was found as the sole product (Scheme 1).



Scheme 1 Depropargylation of Propargylic ether

Conclusions

In conclusion, we have developed a simple, efficient, mild and good alternative catalytic method for the synthesis of primary propargylic alcohols from terminal alkyne. This procedure is far superior with respected to the established methods in terms of (i) simplicity of operation (ii) higher quantity of yields and (iii) faster rate of reaction. We believe that the present methodology for synthesis of primary propargylic alcohols has immense potential for application in both academic and industrial fields**.**

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental details, MS and ^{1}HNMR and ^{13}CNMR for all products]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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