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Hydroxyapatite supported copper catalyst for effective three-component coupling

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Abstract—The coupling of three-components, namely an aldehyde, an alkyne and an amine to prepare propargylamines was performed using copper exchanged hydroxyapatite (CuHAP) as the catalyst under mild reaction conditions and in the absence of any co-catalyst. A variety of aldehydes and amines were converted to the corresponding propargylamines, demonstrating the versatility of the reaction. CuHAP was recovered quantitatively by simple filtration and reused several times.

Metal mediated C–C bond formations are among the most important reactions in organic synthesis.[1] Copper is an essential trace element in all living systems. Due to its redox properties, copper, as a co-factor in many proteins, catalyzes single electron transfer reactions. Propargylamines are important synthetic intermediates for potential therapeutic agents and polyfunctional amino derivatives.[2] However, the standard practice for carrying out such reactions involves the amination of propargylic halides, propargylic phosphates or propargylic triflates.[3] Recently a range of efficient and mild metal-catalyzed reactions based upon the nucleophilic addition of in situ generated metal acetylides to imines and enamines have been reported for the synthesis of propargylamines.[4] Wei and Li have reported the highly efficient three-component coupling reaction through C–H activation in water using gold, silver and silver in ionic liquids without using any noble metal co-catalyst.[5] Nevertheless, the scope is generally limited for cyclic amines in the case of the silver catalyzed reaction, and inert conditions are invariably used for the gold and silver catalyzed reactions in order to obtain good yields. Very recently Tu and co-workers developed microwave augmented three-component coupling reactions of wider scope using CuI as a catalyst, a reaction, which otherwise requires five days under thermal conditions.[6] Despite these advantages of homogeneous metal catalyst, difficulties in recovering the expensive catalyst from the reaction mixture severely obstructs its wide use in industry. Thus, development of improved synthetic methods for the preparation of propargylamines remains an active research area.

Heterogeneous catalysis is particularly attractive as it allows production and ready separation of large quantities of products with the use of a small amount of catalyst. Apatites are metal basic phosphates for which the chemical formula is $M_{10}(PO_4)_6(OH)_2$ [M = divalent metal] and the most typical apatite is calcium hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ (CaHAP). CaHAP attracted wide attention due to its versatile applications in the field of bioceramics, chromatographic adsorbents and acid base catalysis. It has been well established that the Ca^{2+} sites of CaHAP can be replaced by divalent cations such as Sr^{2+}, Ba^{2+}, Pb^{2+}, Cd^{2+} etc.[7] Kaneda and co-workers demonstrated the utility of CaHAP as a solid support for Ru and Pd to perform many organic transformations that including oxidation of alcohols and Heck and Diels–Alder reactions.[8]

Herein we designed and developed a method involving CuHAP for the three-component coupling of aldehydes, amines and alkynes to generate propargylamines without using any co-catalyst or additive (Scheme 1).

Calcium hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] was synthesized according to the literature procedure.[9] CaHAP (1 g) was stirred with aqueous copper acetate (400 mg, 2 mmol in 25 mL water) at 80 °C for a period of 10 h. The slurry obtained was filtered, washed with deionized

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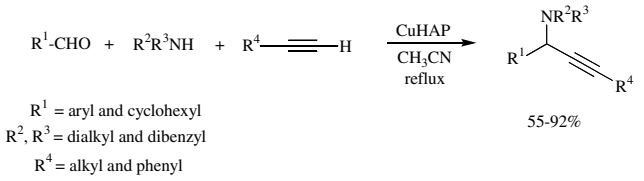
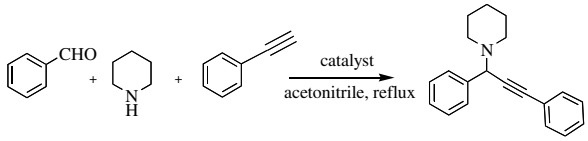


Scheme 1.

water and dried overnight at 110 °C, yielding copper exchanged hydroxyapatite as a blue powder, which was characterized by XPS, SEM-EDAX and IR. XPS analysis of the CuHAP catalyst indicated the same binding energy values for Ca, P and O as in CaHAP. A narrow scan of Cu $2p_{3/2}$ for CuHAP showed the binding energy peak at 934.9 (the binding energy of Cu in Cu(II) is around 935 eV),[10] which indicates copper in the +2 state in CuHAP. The copper content was measured as 1.25 mmol g^{-1} using SEM-EDAX.

In an effort to develop a better catalytic system, various metal hydroxyapatites were screened in the three-component reaction composed of benzaldehyde, piperidine and phenylacetylene in acetonitrile under reflux and the results are summarized in Table 1. FeHAP gave lower yields, while CuHAP and homogeneous $Cu(OAc)_2$ afforded very good yields. When the reaction was conducted with Cu powder, a lower yield was obtained even after longer reaction times. The order of efficiency is CuHAP > $Cu(OAc)_2$ > RuHAP > Cu > FeHAP. The solvent also has a pronounced effect in these reactions. Acetonitrile provided optimum yields, whereas toluene and water offered lower yields. The optimum ratio of aldehyde, amine and alkyne was found to be 1:1.2:1.3. The controlled three-component reaction conducted under identical conditions and devoid of CuHAP gave no coupled product, despite prolonged reaction times. CuHAP was recovered quantitatively by simple filtration and reused several times showing consistent activity even after the fourth cycle (Table 1, entry 3). Moreover the absence of copper in the filtrate was confirmed by AAS, which reiterates that no leaching of copper occurred during the reaction and provides evidence for heterogeneity throughout the reaction.

Table 1. Three-component coupling of benzaldehyde, piperidine and phenylacetylene with different catalysts[a]



Entry	Catalyst	Yield (%)[b]
1	FeHAP	25
2	RuHAP	60
3	CuHAP	85
		80[c]
4	$Cu(OAc)_2$	80
5	Cu powder	45

[a] Benzaldehyde (1 mmol), piperidine (1.2 mmol), phenylacetylene (1.3 mmol), catalyst (100 mg), acetonitrile, reflux, 6 h.
[b] Based on isolated yields.
[c] Yield after fourth cycle.

We chose a variety of structurally divergent aldehydes and amines possessing a wide range of functional groups for our study to understand the scope and the generality of the CuHAP promoted three-component coupling reactions and the results are summarized in Table 2.

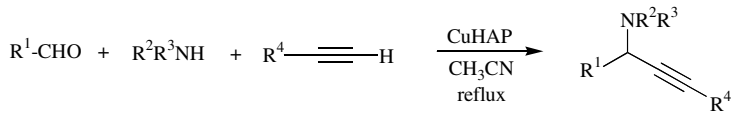
The amines used for this study include aliphatic, alicyclic and aromatic examples. Among the various amines tested, the aliphatic amines piperidine (Table 2, entry 1), pyrrolidine (Table 2, entry 2), morpholine (Table 2, entry 3), dibutylamine (Table 2, entry 4) and the aromatic amine, phenylbenzylamine (Table 2, entry 5), gave very good yields of the coupling product in the three-component system composed of benzaldehyde (Table 2, entries 1–6) or cyclohexylcarboxaldehyde (Table 2, entries 7–11) and phenylacetylene. On the other hand dibenzylamine (Table 2, entry 6) gave the corresponding coupled product in only moderate yield. The order of reactivity for these amines in terms of yields and the reaction time is piperidine > pyrrolidine > dibutylamine > morpholine > phenylbenzylamine > dibenzylamine. (*S*)-Proline methyl ester gave the corresponding chiral propargylamine in good yield (Table 2, entry 12). It is significant that these reactions are faster than that reported using silver in ionic liquids.[5c] Aryl aldehydes possessing an electron-withdrawing group afforded better yields (Table 2, entries 13–15) than that with an electron-donating group (Table 2, entry 16). It is worth noting that 4-nitrobenzaldehyde gave only traces of the coupled product (Table 2, entry 17). When alkylacetylenes were used in place of phenylacetylene, the corresponding propargylamines were isolated in excellent yields (Table 2, entries 18–19).

In conclusion, we have developed a simple and efficient method for the three-component coupling of aldehydes, amines and alkynes in acetonitrile through C–H bond activation at reflux temperature to yield propargylamines with moderate to very good yields using CuHAP as catalyst. The catalyst can be readily recovered and reused thus making this procedure more environmentally acceptable whilst no catalyst leaching was observed. We believe that this methodology will find widespread use in organic synthesis for the preparation of propargylamines.

Typical procedure for three-component coupling reaction with CuHAP. CuHAP (100 mg) was added to a mixture of benzaldehyde (1 mmol), piperidine (1.2 mmol) and phenylacetylene (1.3 mmol) in acetonitrile (3 mL) at reflux, and the mixture was stirred for 6 h. The progress of the reaction was monitored by TLC and on completion the reaction mixture was filtered and the filtrate concentrated under reduced pressure to afford the crude product, which after chromatography on silica gel gave the corresponding propargylamine, *N*-(1,3-diphenyl-2-propynyl)piperidine.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67–7.62 (m, 2H), 7.55–7.50 (m, 2H), 7.40–7.26 (m, 6H), 4.8 (s, 1H), 2.61–2.50

Table 2. Three-component coupling of aldehydes, amines and alkynes using CuHAP as catalyst



Entry	R^1	Amine (R^2, R^3)	R^4	Time (h)	Yield (%)[a,b]
1	Ph	Piperidine	Ph	6	85
2	Ph	Pyrrolidine	Ph	6	85
3	Ph	Morpholine	Ph	6	70
4	Ph	Dibutyl	Ph	5	80
5	Ph	R_2 = Ph, R_3 = $PhCH_2$	Ph	8	65
6	Ph	Dibenzyl	Ph	10	60
7	Cyclohexyl	Piperidine	Ph	4	87
8	Cyclohexyl	Morpholine	Ph	6	80
9	Cyclohexyl	Dibenzyl	Ph	8	70
10	Cyclohexyl	R_2=Ph, R_3=$PhCH_2$	Ph	6	74
11	Cyclohexyl	Dibutyl	Ph	4	80
12	Ph	L-Proline methyl ester	Ph	4	85
13	4-ClC_6H_4	Piperidine	Ph	5	90
14	3,4-$Cl_2C_6H_3$	Dibenzyl	Ph	10	55
15	3,4-$Cl_2C_6H_3$	Piperidine	Ph	8	85
16	4-$MeOC_6H_4$	Piperidine	Ph	18	55
17	4-$NO_2C_6H_4$	Piperidine	Ph	12	5
18	Ph	Piperidine		4	80
19	Cyclohexyl	Piperidine		4	92

[a] Isolated yields.
[b] Identification of the products was by NMR and mass spectrometric analysis.

(m, 4H), 1.70–1.50 (m, 4H), 1.50–1.40 (m, 2H). MS (70 eV) *m/z* (%) 275 (M^+, 18.75%), 274 (8.75%), 202 (11.25%), 198 (72.5%), 191 (100%), 115 (7.5%), 84 (7.5%).

Acknowledgements

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