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Efficient one-pot synthesis of propargylamines using zinc dust

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Abstract—The one-pot synthesis of propargylamines is achieved efficiently via a three component coupling of various aldehydes, alkynes and amines using zinc dust under mild reaction conditions and in the absence of a co-catalyst. Zinc dust was recovered quantitatively by simple centrifugation and reused.

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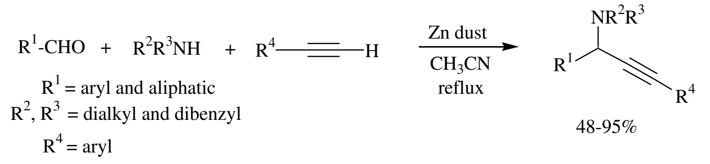
Metal mediated C–C bond formations are important reactions in organic synthesis.[1] One-pot multicomponent coupling reactions (MCR) where several organic moieties are coupled in one step is an attractive synthetic strategy. Propargylamines are important synthetic intermediates[2a–c] for biologically active compounds such as β-lactams, conformationally restricted peptides, isosteres, natural products and therapeutic drug molecules.[2d,e]

Typically, propargylamines are prepared by amination of propargylic halides, propargylic phosphates or propargylic triflates.[3] Recently, 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] Under homogeneous conditions, catalytic systems such as Ag(I) salts,[5] Au(I)/Au(III) salts,[6] Au(III) salen complexes,[7] Cu(I) salts,[8] iridium complexes[9] and Hg_2Cl_2[10] have been used for the three component coupling (3CC) of aldehydes, alkynes and amines to synthesize propargylamines via C–H activation. Silver salts in ionic liquids and gold/silver salts used for such couplings have limitations with cyclic amines.[5d] CuI as catalyst has a wider substrate scope under microwave conditions for the 3CC reaction, which otherwise requires 5 days under thermal conditions.[8a] Despite these advantages of homogeneous metal catalysts, difficulties in recovering the expensive catalyst from the reaction mixture severely inhibits their wide use in industry. 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. Previously, we reported the first heterogeneous 3CC reaction using a hydroxyapatite supported copper catalyst[11] (Cu-HAP), and later the same coupling reaction was also achieved using a layered double hydroxide supported gold catalyst (LDH-$AuCl_4$).[12]

Recently, Kidwai et al. reported an efficient 3CC reaction using gold and copper nanoparticles.[13] The development of improved synthetic methods for the preparation of propargylamines remains an active research area.

Zinc-mediated multicomponent reactions have gained considerable interest in various C–C bond formation



Scheme 1.

Keywords: Zn dust; Propargylamines; Heterogeneous catalyst.

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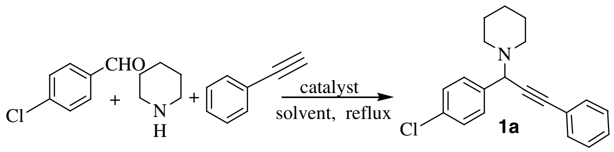
reactions,[14a] Fan et al. reported the Zn dust catalyzed three-component, one-pot benzylation and allylation of aldehydes and amines for synthesis of homobenzylamines and homoallylamines.[14b]

Herein, we report the 3CC reaction of aldehydes, amines and alkynes to generate propargylamines using Zn dust without using any co-catalyst or additive (Scheme 1).

Table 1. Screening of reaction parameters for the synthesis of **1a**[a]



Entry	Catalyst	Solvent	Yield[b] [%]
1	Zn dust	Acetonitrile	95, 87[c]
2	Zn dust	THF	42
3	Zn dust	Dioxane	35
4	Zn dust	Toluene	60
5	Zn dust	Methanol	70
6	Zn dust	Water	25
7	ZnO (nano)	Acetonitrile	52
8	ZnO (commercial)	Acetonitrile	15
9	$ZnBr_2$	Acetonitrile	90
10	$ZnCl_2$	Acetonitrile	87

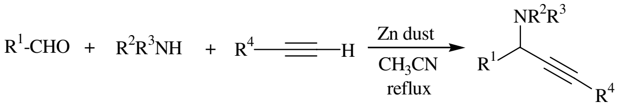
[a] 4-Chlorobenzaldehyde (1 mmol), piperidine (1.1 mmol), phenylacetylene (1.2 mmol), catalyst (15 mol %), acetonitrile, reflux, 8 h.
[b] Based on isolated yields.
[c] Yield after fourth cycle.

The simplicity of the procedure lies in the fact that no activation of the Zn dust was required.

In an effort to develop an optimal catalytic system, various reaction parameters were studied for the preparation of *N*-[1-(4-chlorophenyl)-3-phenyl-2-propynyl]-piperidine via reaction of 4-chlorobenzaldehyde, piperidine and phenylacetylene in solvent under reflux and the results are summarized in Table 1. The solvent had a pronounced effect on these reactions (Table 1, entries 1–6), acetonitrile providing good yields whereas methanol and toluene afforded only moderate yields of the desired product. Various Zn-based catalysts such as Zn dust, $ZnBr_2$, $ZnCl_2$, ZnO (commercial) and nanocrystalline ZnO were screened for the 3CC reaction. Zn dust was found to be the most effective catalyst (Table 1, entries 1 and 7–10). The optimum ratio of aldehyde, amine and alkyne was 1:1.1:1.2. The control 3CC reaction conducted under identical conditions and devoid of Zn dust gave no coupled product, despite prolonged reaction times. Zn dust was recovered quantitatively by simple centrifugation and reused several times, showing consistent activity even after the fourth cycle (Table 1, entry 1).

We chose a variety of structurally diverse aldehydes and amines possessing a wide range of functional groups for our study to understand the scope and the generality of the Zn dust promoted 3CC reactions and the results are summarized in Table 2. Aliphatic amines such as piperidine, pyrrolidine, morpholine, diallylamine and dibenzylamine gave good yields of the coupling product in the three-component system composed of 4-chlorobenz-

Table 2. One-pot synthesis of propargylamines using Zn dust as catalyst[a]



Entry	R^1	Amine [R^2, R^3]	R^4	Time [h]	Yield[b,c] [%]
1	Ph	Piperidine	Ph	9	90
2	Ph	Pyrrolidine	Ph	9	88
3	Ph	Morpholine	Ph	9	87
4	4-ClC_6H_4	Morpholine	Ph	9	91
5	4-ClC_6H_4	Piperidine	Ph	8	95
6	4-ClC_6H_4	Diallylamine	Ph	12	75
7	4-ClC_6H_4	Dibenzylamine	Ph	12	78
8	4-CNC_6H_4	Piperidine	Ph	9	90
9	$4\text{-CH}_3OC_6H_4$	Piperidine	Ph	14	48
10	2-Furfuryl	Piperidine	Ph	9	87
11	2-Thienyl	Piperidine	Ph	9	85
12	$CH_3(CH_2)_3$	Piperidine	Ph	11	74
13	$(CH_3)_2CHCH_2$	Piperidine	Ph	10	79
14	Cyclohexyl	Piperidine	Ph	12	75
15	Ph	Piperidine	$4\text{-CH}_3OC_6H_4$	12	84
16	4-ClC_6H_4	Piperidine	$4\text{-CH}_3OC_6H_4$	12	88
17	4-ClC_6H_4	Morpholine	$4\text{-CH}_3OC_6H_4$	12	85
18	4-ClC_6H_4	Piperidine	$4\text{-CH}_3C_6H_4$	12	78
19	$4\text{-NO}_2C_6H_4$	Piperidine	Ph	12	—

[a] Aldehyde (1 mmol), amine (1.1 mmol), alkyne (1.2 mmol), catalyst (15 mol %), acetonitrile, reflux.[16]
[b] Isolated yields.
[c] The products were identified by NMR and mass spectrometric analysis.

aldehyde (Table 2, entries 4–7) or aliphatic aldehydes (Table 2, entries 12 and 13) and phenylacetylene. Dibenzylamine and diallylamine (Table 2, entries 6 and 7) show little difference in the yield compared to other aliphatic amines.

The order of reactivity for these amines in terms of yields and the reaction time was piperidine > pyrrolidine > morpholine > dibenzylamine > dially amine. Amongst the various aldehydes tested (aliphatic, aromatic and heteroaromatic aldehydes), aryl aldehydes possessing an electron-withdrawing group such as 4-cyanobenzaldehyde afforded better yields (Table 2, entry 8) than those with an electron-donating group such as 4-methoxybenzaldehyde (Table 2, entry 9). Heteroaromatic aldehydes such as furfuraldehyde and 2-thiophenecarboxaldehyde reacted with piperidine and phenylacetylene to afford the corresponding propargylamines in good yields. The reactivity of aliphatic aldehydes such as cyclohexanecarboxaldehyde, valeraldehyde and isovaleraldehyde was low compared to aromatic aldehydes (Table 2, entries 12–14). There was not much difference in the yield when the aryl group of the phenyl acetylene was substituted with a 4-methoxy or 4-methyl group (Table 2, entries 15–18).

It is assumed that zinc forms a zinc acetylide intermediate[15] by the C–H bond activation of the alkyne. The zinc acetylide intermediate thus generated will react with the iminium ion prepared in situ from the aldehyde and the amine and form the corresponding propargylamine, water and metallic zinc. Thus the regenerated zinc participates further in the reaction and completes the catalytic cycle.

In conclusion, we have developed a simple and efficient method for the three-component coupling of aldehydes, amines and alkynes in acetonitrile at reflux to yield propargylamines in moderate to very good yields using Zn dust. Zinc dust can be readily recovered and reused thus making this procedure more environmentally acceptable. We believe that this methodology will find widespread use in organic synthesis for the preparation of propargylamines.

Acknowledgement

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16. *Typical procedure for the 3CC reaction:* Zn dust (10 mg or 15 mol %) was added to a mixture of 4-chlorobenzaldehyde (1 mmol), piperidine (1.1 mmol) and phenylacetylene (1.2 mmol) in acetonitrile (3 mL) at reflux, and the mixture was stirred for 8 h. The progress of the reaction was monitored by TLC and on completion, the reaction mixture was centrifuged and the centrifugate was concentrated under reduced pressure to afford the crude product, which after chromatography on silica gel (100–200 mesh) using hexane/ethyl acetate, 90/10, gave the corresponding propargylamine, *N*-[1-(4-chlorophenyl)-3-phenyl-2-propynyl]piperidine. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57–7.54 (m, 2H), 7.49–7.45 (m, 2H), 7.31–7.28 (m, 5H), 4.72 (s, 1H), 2.54–2.5 (m, 4H), 1.62–1.54 (m, 4H), 1.5–1.45 (m, 2H), ESI MS (*m*/*z*): 310 $(M+H)^+$.