

Ultrasound-assisted rapid and efficient synthesis of propargylamines

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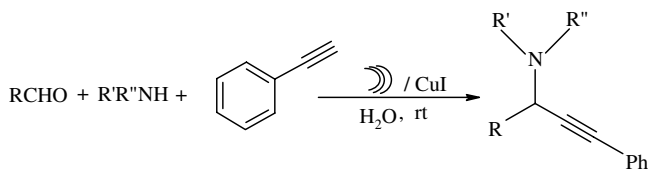
Abstract—Ultrasound was used for the addition of metal acetylides to in situ generated imines to generate propargylamines in good to excellent yields using copper iodide in water at ambient temperature. This process is an efficient alternative to traditional heated reactions. A variety of aldehydes and amines were used for this reaction.
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Multi-component coupling reactions in one pot are an attractive strategy in organic synthesis.¹ Three-component coupling of an aldehyde, an alkyne and an amine (A^3 coupling) is one of the best examples and has received much attention in recent times.² The resultant propargylamines obtained by the A^3 coupling reaction are important synthetic intermediates for potential therapeutic agents and polyfunctional amino derivatives.³ The three-component coupling reactions can be carried out either by amination of propargylic halides, propargylic triflates or nucleophilic addition of in situ generated metal acetylides. By using the latter procedure, the A^3 coupling reaction can be catalyzed by several transition metal catalysts via C–H activation. Silver salts,⁴ gold salts,⁵ copper salts,⁶ Ir complexes⁷ and a Cu/Ru⁸ bimetallic system under homogeneous conditions have all been used for this reaction and later their chiral equivalents were also reported.⁹ Recently an A^3 coupling reaction was reported by Li and co-workers,¹⁰ using immobilization of silver salts in ionic liquids whilst Choudary et al.,¹¹ reported the same using copper-supported hydroxyapatite.

Ultrasound accelerated chemical reactions are well known and proceed via the formation and adiabatic collapse of transient cavitation bubbles.¹² Ultrasonic irradiation can be utilized as an alternative energy source for organic reactions ordinarily accomplished by heating. It increases the reaction rate many fold when com-

pared with conventional reaction conditions. It is also known to accelerate diverse types of organic reactions and it is established as an important technique in organic synthesis. Many reactions have been conducted with homogeneous and heterogeneous catalysts, in which the rate of the reaction was accelerated by sonication. Several reports on versatile reactions carried out using ultrasonication include a low temperature Heck reaction with Pd/C by Samant et al.,¹³ Reformatsky reactions by Bartsch and co-workers,¹⁴ sonochemical preparation of ionic liquids by Varma et al.¹⁵ and Sonogashira coupling by Gholap et al.¹⁶

Herein, we report an efficient method for the preparation of propargylamines using ultrasound as the energy source by simple exposure of the reactants in a container to irradiation using a laboratory sonication bath. This approach requires a shorter reaction time at ambient temperature in contrast to the several hours needed under conventional heating conditions and avoids the use of organic solvents as the reaction medium. Ultrasound was used for the addition of the metal acetylide to in situ generated imines to generate propargylamines (Scheme 1).



Scheme 1.

Keywords: Ultrasonication; A^3 coupling; Propargylamine; Water; Copper salt.

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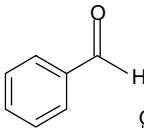
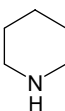
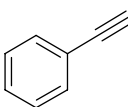
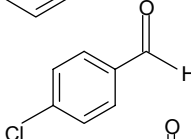
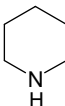
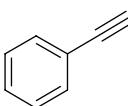
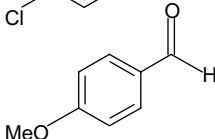
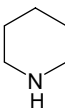
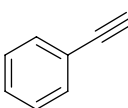
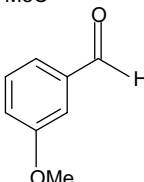
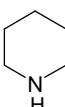
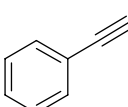
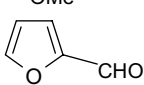
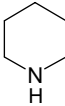
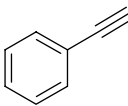
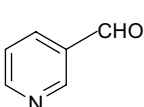
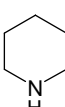
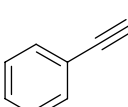
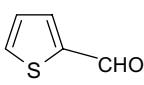
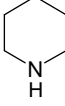
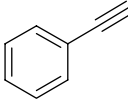
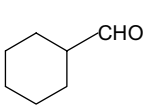
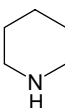
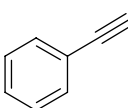
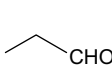
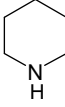
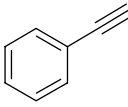
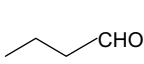
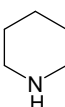
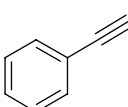
Table 1. Screening of Cu salts for the three-component coupling reaction between benzaldehyde, piperidine and phenyl acetylene in water^a

Entry	Catalyst	Yield ^b (%)
1	CuI	98
2	CuCl	48
3	CuOTf	36
4	CuCl ₂	No reaction
5	Cu(acac) ₂	No reaction
6	Cu(OAc) ₂	No reaction
7	Cu-phthalocyanine	No reaction
8	Cu(NO ₃) ₂	No reaction

^a Reaction conditions as exemplified in the typical experimental procedure.^b Yields are based on ¹H NMR integration.

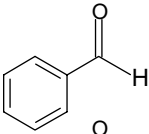

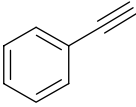
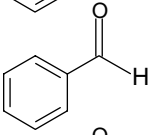
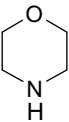
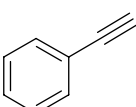
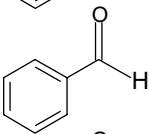
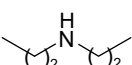
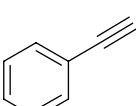
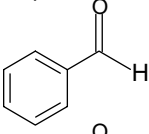
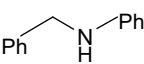
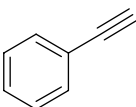
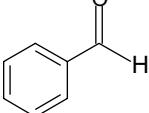
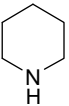
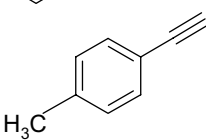
Initially, in an effort to develop an improved catalytic system for the synthesis of propargylamines in water by the three-component coupling of an aldehyde, an alkyne and an amine, various copper salts (15 mol %) were screened to optimize the reaction conditions and the results are shown in Table 1. All the reactions were carried out with a mixture of benzaldehyde, piperidine, phenylacetylene and Cu salt (15 mol %) in water under sonication for 45 min. Among the different Cu(I) and Cu(II) salts assayed, no reaction was observed with Cu(II) salts (entries 4–8) whilst Cu(I) salts (entries 1–3) gave varying yields. CuI (entry 1) was found to be most effective in catalyzing the three-component coupling reaction. The copper displaces the proton of the phenyl

Table 2. Three-component coupling reaction of an aldehyde, an amine and an alkyne^a

Entry	Aldehyde	Amine	Alkyne	Time (min)	Yield ^b
1				45	98
2				45	55
3				75	25
4				75	34
5				45	96
6				45	60
7				45	94
8				45	98
9				45	98
10				45	98

^a Reaction conditions as exemplified in the typical experimental procedure.^b Yields are based on ¹H NMR integration.

Table 3. Three-component coupling reaction between benzaldehyde and phenyl acetylene with various amines^a

Entry	Aldehyde	Amine	Alkyne	Time (min)	Yield ^b
1				45	98
2				45	98
3				45	55
4				45	86
5				45	98

^a Reaction conditions as exemplified in the typical experimental procedure.^b Yields are based on ¹H NMR integration.

acetylene to form phenyl acetylide, which reacts with the iminium ion generated in situ from the aldehyde and amine to give the corresponding propargylamine.

Subsequently, a variety of propargylamines were prepared from various aldehydes, alkynes and amines using the optimized conditions and the results are summarized in Table 2 (entries 1–10). As can be seen from the table, the aromatic (entry 1) and heteroaromatic (entries 5 and 7) aldehydes underwent addition to afford the corresponding propargylamine in excellent yields, whereas only a trace amount of product was obtained with aldehydes bearing electron withdrawing and donating groups under similar experimental conditions (entries 2, 3 and 4). Methoxy-substituted aldehydes gave lower yields even after longer reaction times. Aliphatic aldehydes (entries 9 and 10), on the other hand, displayed higher reactivity and gave both higher conversions and greater yields.

To extend the scope of the reaction, various amines were reacted with benzaldehyde and phenylacetylene in the presence of CuI and the results are tabulated in Table 3. Among the amines, pyrrolidine and morpholine (entries 1 and 2) gave excellent yields of the propargylamines, whereas dibutylamine formed the corresponding product in moderate yield (entry 3). *N*-Phenylbenzylamine (entry 4) also reacted smoothly under these conditions. Even when using 4-methylphenylacetylene as the terminal alkyne (entry 5) the reaction afforded the corresponding propargylamine in excellent yield.

In summary, an ultrasound-promoted, rapid and efficient three-component reaction for the preparation

of propargylamines using CuI as the catalyst in water in short reaction times has been developed. This room temperature protocol is an environmental friendly process, and provides a diverse range of propargylamines in good to excellent yields with water as the only by-product.

Typical procedure for the *A*³ coupling reaction: A mixture of benzaldehyde (106 mg, 1 mmol), piperidine (102 mg, 1.2 mmol), phenylacetylene (153 mg, 1.5 mmol) and CuI (0.015 g, 0.0015 mol) in water (3 mL) was sonicated for 45–75 min in a laboratory ultrasonic cleaning bath. After completion of the reaction (as monitored by TLC) the catalyst was filtered through Celite. The product was extracted using ethyl acetate. After removing the solvent under vacuum, the crude material was purified by chromatography on silica gel to afford pure *N*-(1,3-diphenyl-2-propynyl)piperidine.

Data for *N*-(1,3-diphenyl-2-propynyl)piperidine (Table 2, entry 1): ¹H NMR (200 MHz, CDCl₃): δ 1.30–1.80 (m, 6H), 2.42–2.83 (m, 4H), 4.92 (s, 1H), 7.10–7.80 (m, 10H). MS (EI) *m/z* 275 (26%), 198 (85%), 191 (100%), 77 (28%).

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