Base-Catalyzed, Three-Component Coupling of Aldehydes, Terminal Aryl Acetylenes, and Amines: Application to Synthesis of Propargylamines

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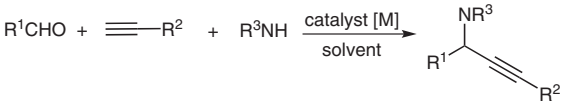
Abstract: Propargylamines are formed in high yield by three-component coupling reaction of aldehydes, terminal aryl acetylenes, and amines in DMSO in the presence of catalytic tetraalkylammonium hydroxide. This reaction does not require a transition-metal catalyst.

Key words: three-component coupling, aldehydes, aryl acetylenes, amines, tetraalkylammonium hydroxide

One-pot multicomponent coupling reactions (MCR) have attracted significant research interest in recent years.[1] Multicomponent reactions can provide ideal protocols for the development of environmentally friendly and economically advantageous chemical processes.[2] Recently, a Barbier–Grignard-type addition of alkynes to imines to generate propargylamines in water/organic solvent by using a transition-metal catalyst has been reported (Scheme 1).



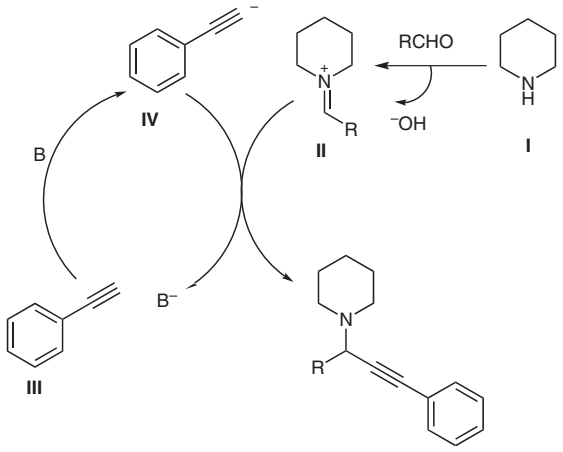
Scheme 1

Transition metals such as silver,[3] ruthenium,[4] copper,[5] indium,[6a] nickel,[6b] iron,[7] and gold[8] have been used to catalyze the addition of terminal alkynes to imines to afford propargylamines in high yield. The microwave-promoted Mannich condensation of terminal alkynes and secondary amines has also been reported.[9] However, all these methods have the drawback of requiring catalyst separation to limit the metallic impurity.

Propargylamines are versatile building blocks in organic synthesis and important structural elements of natural products and therapeutic drug molecules.[10] Recently, it was reported that the high acidity of aryl acetylenes in dimethylsulfoxide[11–15] should allow formation of the reactive acetylide species by treatment of the terminal alkynes with a hydroxide or alkoxide base in dimethylsulfoxide. In fact, formation of acetylide intermediates has been proposed by Ishikawa and co-workers in their studies of the alkynylation of ketones.[15] We have applied this hypothesis to the three-component coupling reaction of aldehydes, terminal aryl acetylenes, and amines in DMSO for synthesis of propargylamines.

In the initial study, piperidine, benzaldehyde, and phenylacetylene were chosen to optimize the reaction conditions. Following optimization, 10 mol% of tetrabutylammonium hydroxide (TBAOH) was found to be effective for the formation of propargylamines in DMSO at room temperature.

The mechanistic pathway of this TBAOH-catalyzed synthesis of propargylamines in DMSO is proposed in (Scheme 2). Reversible activation of the C–H bond of phenylacetylene (**III**) by the base generates acetylide intermediate (**IV**) which reacts with imminium ion (**II**) generated in situ from the aldehyde and secondary amine (**I**) to give the corresponding propargylamine and regenerate catalyst for further reaction.



Scheme 2

The scope of the process was examined as illustrated by the examples in Table 1. Aromatic and aliphatic aldehydes bearing functional groups such as alkoxy, chloro, and trifluromethyl were found to undergo the three-component coupling reaction. Aryl aldehydes bearing the electron-donating methoxy group reacted smoothly but required longer reaction time; whereas aryl aldehydes bearing electron-withdrawing groups displayed high reactivity and higher conversion with shorter reaction time. The coupling of cyclohexylcarboxaldehyde was also facile (entries 11 and 12). Pyridine-4-carboxaldehyde (entry 6) gave an excellent yield, while pyridine-2-carboxalde-

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hyde (entry 5) formed the requisite propargylpyridine with a small amount of byproduct (20% isolated based on aldehyde), identified as 3-phenyl-1-(piperidin-1-yl)indolizine (Figure 1), which is formed by isomerization of the propargylpyridine. In addition, 2-furaldehyde (entries 9 and 10) also gave good yields (82% and, 85% respectively). The reaction involving phenylacetylene gave both higher conversions and better yields, while 4-nitrophenylacetylene gave a lower yield (entry 13), which could be a reflection of the reduced nucleophilicity of the acetylide anion. Alkyl acetylenes (entry 14) failed to react under the optimized conditions, probably due to their lower acidity. To expand the scope of amine substrates, we used various aldehydes and phenylacetylene as model substrates and examined various primary and secondary amines. It was found that dialkylamines reacted smoothly under the optimized conditions, however, use of a bulky amine led to lower yield of product (entry 16).

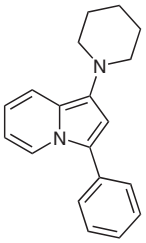

Figure 1

In conclusion, we have developed a TBAOH-catalyzed three-component coupling of aldehydes, terminal aryl acetylenes, and amines via C–H activation in DMSO under transition-metal-free conditions. The process is simple and has been shown to generate a diverse range of propargylamines in excellent yields. The experimental simplicity, ease of product isolation, low cost, and ready availability of reagents should make this process useful for the synthesis of propargylamines.

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Reference and Notes

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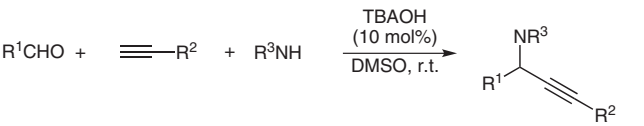
Table 1 Coupling of Aldehydes, Amines, and Alkynes Catalyzed by Tetrabutylammonium Hydroxide in DMSO



Entry	**1** (R^1)	**2** (R^2)	Amine	Product **3**	Yield (%)[a]	Time (min)
1	Ph	Ph	piperidine	**3a**	90	30
2	4-$MeOC_6H_4$	Ph	piperidine	**3b**	89	230
3	4-$F_3CC_6H_4$	Ph	piperidine	**3c**	76	20
4	4-ClC_6H_4	Ph	piperidine	**3d**	84	20
5	2-pyridine	Ph	piperidine	**3e**	45	120
6	4-pyridine	Ph	piperidine	**3f**	75	20
7	4-$O_2NC_6H_4$	Ph	morpholine	**3g**	82	30
8	Ph	Ph	pyrrolidine	**3h**	92	40
9	furaldehyde	Ph	piperidine	**3i**	82	45
10	furaldehyde	Ph	morpholine	**3j**	85	45
11	cyclohexyl	Ph	piperidine	**3k**	73	30
12	cyclohexyl	Ph	morpholine	**3l**	70	30
13	Ph	4-$O_2NC_6H_4$	morpholine	**3m**	37	240
14	Ph	Bu	morpholine	**3n**	0	360
15	Ph	Ph	Et_2NH	**3o**	75	30
16	Ph	Ph	Et_2NH	**3p**	20	360

[a] Isolated yield with respect to aldehyde.

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(16) **General Procedure for the Synthesis of Propargylamines**

A 25 mL round-bottom flask was charged with DMSO (3 mL), aldehyde (1.0 mmol), amine (1.3 mmol), alkyne (1.3 mmol), and TBAOH (0.1 mmol). The resulting solution was stirred at r.t., for the time indicated in Table 1. The reaction mixture was poured into H_2O (60 mL), and the suspension was stirred for 30 min. Then, it was extracted with EtOAc (2 × 25 mL), and the combined organic extracts were dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the crude products. Purification by silica gel column chromatography (hexane–EtOAc) gave pure materials.

Representative Spectroscopic Data

***N*-(1,3-Diphenyl-2-propynyl)piperidine (3a)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.60 (m, 2 H), 7.53–7.50 (m, 2 H), 7.37–7.27 (m, 6 H), 4.79 (s, 1 H), 2.56 (m, 4 H), 1.61–1.56 (m, 4 H), 1.45–1.44 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 131.6, 128.5, 128.2, 128.0, 127.4, 123.2, 87.6, 86.0, 62.3, 26.8, 26.1, 24.4. MS: *m/z* (%) = 275 (20) [M$^+$], 198 (81), 191 (100), 115 (14).

***N*-[1-(4-Methoxyphenyl)-3-phenyl-2-propynyl]-piperidine (3b)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.50 (m, 4 H), 7.33–7.30 (m, 3 H), 6.90–6.87 (m, 2 H), 4.74 (s, 1 H), 3.80 (s, 3 H), 2.56–2.54 (m, 4 H), 1.64–1.53 (m, 4 H), 1.46–1.42 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 131.7, 130.6, 129.6, 128.2, 128.0, 123.3, 113.3, 87.6, 86.3, 61.7, 55.2, 50.6, 26.1, 24.4. MS: *m/z* (%) = 307 (4) [M$^+$], 221 (38), 135 (30), 87 (100), 43 (73).

***N*-(1,3-Diphenyl-2-propynyl)pyrrolidine (3h)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.66 (m, 2 H), 7.56–7.53 (m, 2 H), 7.37–7.30 (m, 6 H), 4.90 (s, 1 H), 2.72 (m, 4 H), 1.81 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 131.5, 128.2, 128.1, 127.5, 123.1, 86.8, 86.6, 59.0, 50.2, 23.4. MS: *m/z* (%) = 261 (8) [M$^+$], 184 (61), 115 (13).

***N*-1[(4-Cyclohexyl-3-phenyl-2-propynyl)]morpholine (3l)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.44 (m, 2 H), 7.29–7.28 (m, 3 H), 3.79–3.74 (m, 4 H), 3.13 (d, *J* = 9.9 Hz, 1 H), 2.70–2.69 (m, 2 H), 2.53–2.50 (m, 2 H), 2.14–2.04 (m, 2 H), 1.77–1.59 (m, 4 H), 1.32–0.96 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.6, 128.1, 127.7, 123.3, 86.7, 86.5, 67.0, 63.8, 49.8, 38.9, 30.9, 30.2, 26.6, 26.1, 25.9. MS: *m/z* (%) = 283 (5) [M$^+$], 200(100), 115 (20), 77 (2), 55 (9), 41 (10).