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Catalyst-free activation of methylene chloride and alkynes by amines in a three-component coupling reaction to synthesize propargylamines†

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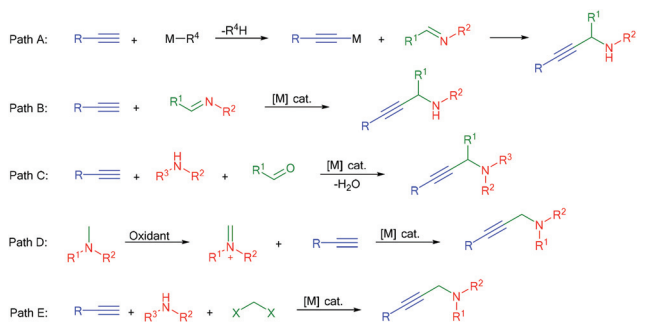
Propargylamines are synthesized *via* metal-free activation of the C–halogen bond of dihalomethanes and the C–H bond of terminal alkynes in a three-component coupling without catalyst or additional base and under mild reaction conditions. The dihalomethanes are used both as solvents as well as precursors for the methylene fragment (C_1) in the final product. The scope of the reaction and the influence of various reaction variables has been investigated. A plausible reaction mechanism is proposed and the involvement of various intermediates that can be generated *in situ* in the process is discussed. The metal-free conditions also make this protocol environmentally benign and atom economical.

Introduction

Over the decades, propargylamine derivatives have attracted great attention in organic synthesis, which can mainly be attributed to their wide application in medicinal and synthetic chemistry.[1] The various protocols that have been developed for the synthesis of propargylamines (Scheme 1) include the addition of stoichiometric alkynyl nucleophiles to imines (Path A),[2] transition metal-catalyzed addition of alkynes to imines (Paths B and C),[3] and transition metal-catalyzed oxidative functionalization of tertiary amines (Path D).[4]

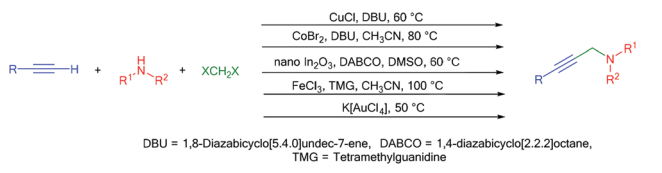


Scheme 1 Various procedures for the synthesis of propargylamines.

Although these are effective methods, they require the presence of a leaving group or the formation of an imine from an aldehyde and an amine (preformed or *in situ*), or an aryl/benzyl-substituted tertiary amine having at least one methyl group.

Direct C–H activation is one of the most atom economical and green reactions for C–C bond formation in modern synthetic chemistry.[5] Recently, an alternative transition metal-catalyzed activation of the C–H bond of alkynes and the C–X bond of dihalomethanes for reaction with amines in a three-component coupling to synthesize propargylamines has also been reported (Path E).[6] The following catalytic systems have been used for this purpose: CuCl/DBU,[6a] $CoBr_2$/DBU,[6b] nano In_2O_3/DABCO,[6c] $FeCl_3$/TMG[6d] and K[$AuCl_4$][6e] (Scheme 2). The advantages of these methods over others are simple operation, mild conditions, and good to excellent yields.

The proposed mechanism for this protocol is depicted in Scheme 3.[6a] There are two plausible pathways for this three-component coupling: one proceeds *via* the intermediacy of a propargylhalide that forms due to the interaction of the dihalomethane with the metal-alkynyl complex; this propargylhalide further reacts with amines to give propargylamines (Path F). The other pathway involves the formation of an iminium ion



Scheme 2 Transition metal-catalyzed synthesis of propargylamines *via* activation of the C–H bond of alkynes and the C–X bond of dihalomethanes.

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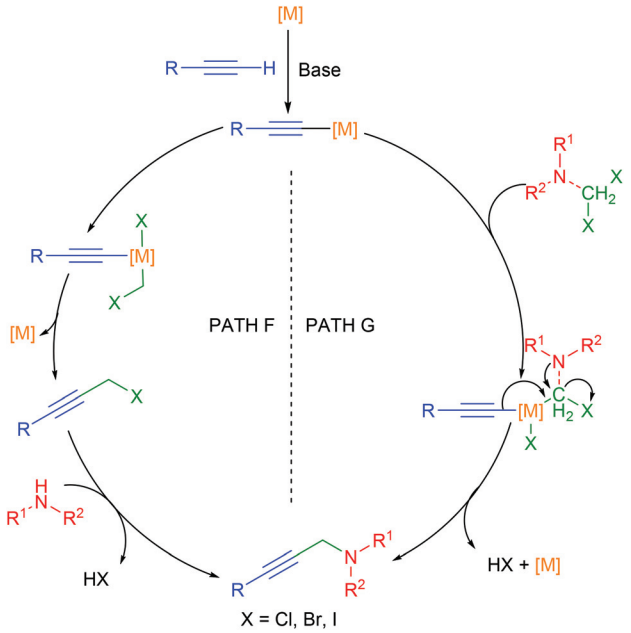


Scheme 3 The proposed mechanism for the three-component coupling to give propargylamines.

intermediate *via* interaction of the dihalomethane with the amine; the reaction of this iminium ion with the metal-alkynyl complex results in propargylamines (Path G).

By using various experimental and spectroscopic methods, it has been proved that Path G is operative in the copper-catalyzed reaction,[6a] and Path F is operative in the iron-[6d] and gold[6e]-catalyzed reactions. From these studies, it is evident that the presence of a catalyst is essential for initial C–H activation of alkynes and for the reaction to proceed further. However, during our studies on the application of magnetic nanoparticles to similar processes, we surprisingly found that a catalyst is not needed for this transformation and thus, herein we would like to report a novel metal-free synthesis of propargylamines *via* a three-component coupling (AHA).

Results and discussion

Among commercially available dihalomethanes, methylene chloride has been chosen as a model substrate for these studies. Methylene chloride is a relatively inert volatile organic liquid that has been used extensively as a solvent in synthesis and extraction processes.[7] Despite its vast utilization as a solvent, there are few published reports on its role as a reactant.[8] In particular, the reaction of methylene chloride with amines has been studied from a kinetic and mechanistic point of view,[8] and it has been established that certain secondary and tertiary amines react with dichloromethane resulting in hydrochloride salts, aminals and/or quaternary salts. However, the reaction rates are very sluggish with half-lives of many weeks to several months.[8] Later, the reaction rate was accelerated by using high temperature or pressure,[9] and Wulff *et al.* also isolated chloromethyl-triethylammonium chloride from the reaction of triethylamine with dichloromethane (Menschutkin reaction) and confirmed its identity by proton NMR.[8c] Further, it was established that the reaction of methylene chloride with a secondary amine results in the corresponding chloromethylamine, iminium ion and methylene-bisamine (aminal) in an equilibrium (Scheme 4).[10]

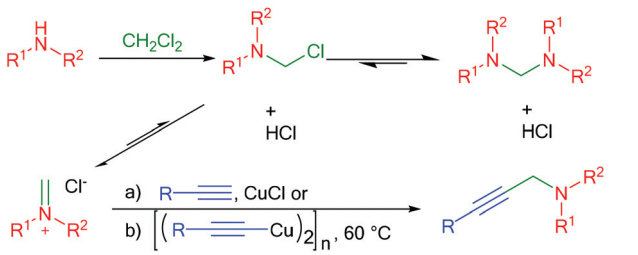
Aminals react as electrophiles with a variety of nucleophiles, such as ketones (Mannich addition),[11a] aldehydes,[11b] phenols,[11c] esters,[9b] indoles[12a] and 2,6-diethyl-4,4-difluoro-1,3,5,7,8-pentamethyl-4-bora-3a,4a-diaza-*s*-indacene (BODIPY),[12b] and are also used in the synthesis of natural products.[12c,d] A similar reaction with copper acetylide resulted in the formation of propargylamines (Scheme 4).[13]

Initially, to optimize the reaction conditions, phenylacetylene, dichloromethane and piperidine were used as model substrates, and the influence of various reaction variables such as the base, solvent and temperature on the reaction was investigated (Table 1). It was observed that the best results were obtained by using dichloromethane as solvent at 70 °C, with an isolated yield of 72% of **4a** (Table 1, entry 28).

Both the addition of bases and the use of other solvents were completely ineffective for this transformation, so either no **4a** or a very low yield (Table 1, entries 1–24) was obtained. The inhibitory effect of various solvents on this reaction can be explained on the basis of solvation of the amine, which is quite facile especially in the case of protic solvents, and results in the formation of hydrogen bonds between the amine and the solvent,[14] consequently weakening the nucleophilic character of the amine and leading to a slower reaction rate.[8a,14]

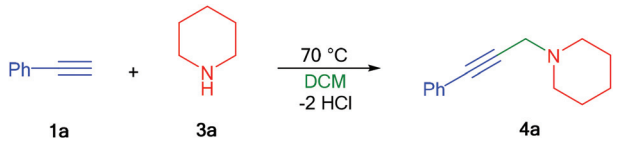
Moreover, it was observed that this reaction was susceptible to temperature changes. At room temperature the yield of **4a** was 15% (Table 1, entry 25), which increased to 72% at 70 °C (Table 1, entry 28). This may be attributed to the fact that the reaction between amines and dichloromethane is slower at low temperature, however an increase in temperature generates a high pressure inside the pressure vial (as reported by Songstad *et al.*), resulting in a higher reaction rate under high pressure.[8a] However, any further increase in temperature above 70 °C does not affect the reaction outcome.

Notably, there was no appreciable difference in the yield with any of the three commercially available dihalomethanes used (Table 1, entries 28, 30, 31). Finally, the reaction mixture was analyzed *via* inductively coupled plasma atomic emission



Scheme 4 The proposed mechanism for copper-catalyzed three-component coupling to propargylamines.

Table 1 Optimization of reaction conditions for the three-component coupling to give propargylamines[a]

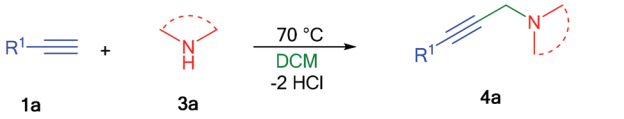


1a 3a 4a

Entry	Solvent	Base	Temp. (°C)	Yield[b] (%)
1	DCM	Et_3N	40	15
2	DCM	DBU	40	20
3	DCM	DABCO	40	27
4	DCM	K_2CO_3	40	30
5	DCM	Na_2CO_3	40	15
6	DCM	$NaHCO_3$	40	0
7	DCM	NaOMe	40	0
8	DCM	*t*-BuOK	40	0
9	DCM	K_3PO_4	40	0
10	DCM	NaOH	40	0
11	DCM	KOH	40	0
12	DCM	—	40	35
13	DMF	—	40	0
14	DMSO	—	40	0
15	CH_3CN	—	40	0
16	MeOH	—	40	0
17	THF	—	40	0
18	H_2O	—	40	0
19	Dioxane	—	40	0
20	Toluene	—	40	0
21	$EtNO_2$	—	40	0
22	Hexane	—	40	0
23	EtOAc	—	40	0
24	DCE	—	40	10
25	DCM	—	25	15
26	DCM	—	50	42
27	DCM	—	60	55
28	DCM	—	70	72
29	DCM	—	80	72
30	DBM	—	70	75[c]
31	DIM	—	70	78[d]

[a] Reaction conditions: phenyl acetylene (1.0 mmol), piperidine (3.2 mmol), base (2.2 mmol) and dichloromethane (2.0 mmol) in 2 mL solvent for 12 h. [b] Isolated yield. [c] Reaction with dibromomethane. [d] Reaction with diiodomethane.

Table 2 Scope of the synthesis of propargylamines[a]



1a 3a 4a

Entry	R^1	Amine	Yield[b] (%)
1	Ph	Piperidine	72
2	Ph	Pyrrolidine	68
3	Ph	Dimethylamine	70
4	Ph	Diethylamine	65
5	Ph	Dibutylamine	62
6	Ph	Diisopropylamine	0
7	Ph	Aniline	0
8	Ph	Butan-1-amine	0
9	4-Methylphenyl	Piperidine	78
10	4-Methylphenyl	Pyrrolidine	72
11	4-Methylphenyl	Dimethylamine	68
12	4-Methylphenyl	Diethylamine	66
13	4-Methylphenyl	Dibutylamine	62
14	4-(*tert*-Butyl)phenyl	Piperidine	83
15	4-(*tert*-Butyl)phenyl	Dibutylamine	70
16	2-(6-Methoxynaphthyl)	Diethylamine	72
17	4-Bromophenyl	Piperidine	65
18	3-Fluorophenyl	Dimethylamine	57
19	3-Fluorophenyl	Diethylamine	54
20	3-Fluorophenyl	Dibutylamine	50
21	3-Ethynylphenyl	Dibutylamine	50
22	Hexyl	Piperidine	0
23	Pentyl	Piperidine	0

[a] Reaction conditions: alkyne (1 mmol) and amine (3.2 mmol) in 5 mL dichloromethane at 70 °C for 12 h. [b] Isolated yield.

spectroscopy (ICP-AES) for a broad range of transition metals including cobalt, copper, platinum, *etc.* However, none of these metals were present in concentrations above a level of 0.1 ppm, which confirms that this reaction is not metal-catalyzed.

After establishing the optimized reaction conditions (Table 1, entry 28), we further explored the generality and functional group compatibility of this protocol using various structurally diverse alkynes and amines, and the results are shown in Table 2.

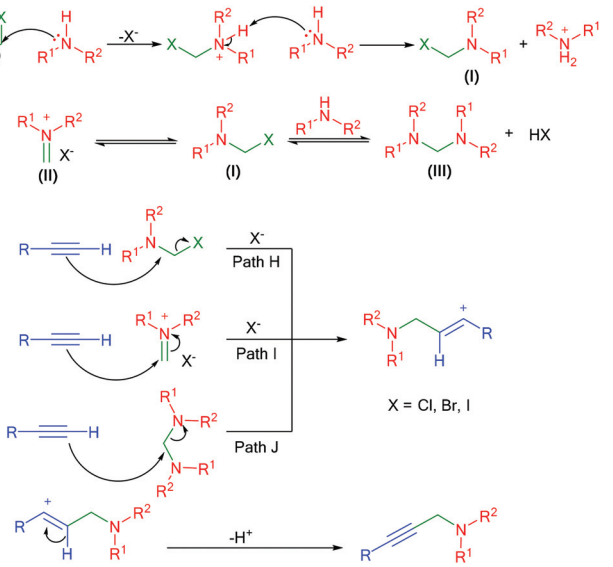
The reaction proceeds smoothly with various aryl acetylenes and amines to afford the corresponding propargylamines in good to excellent yields. However, the output of the reaction favors alkynes with electron-donating substituents. Generally, amines with alkyl substituents that are conformationally restricted such as dimethylamine, piperidine and pyrrolidine[8d,e,15] are more reactive, which can be attributed to the easy accessibility of the lone pair of electrons on the nitrogen of such amines. Hence, these amines showed an excellent conversion rate to the corresponding propargylamines.

Among the acyclic amines, the reaction rate is found to depend on the steric influence of the attached alkyl groups in the order dimethylamine > diethylamine > dibutylamine. Consequently, diisopropylamine reacts very slowly under the optimized reaction conditions, and no product was obtained (Table 2, entry 6).[6d,8a,d,e]

Due to the low basicity of primary (aromatic and aliphatic) amines, the reaction rate with dichloromethane was much slower when compared to secondary amines, and no product was formed in these cases (Table 2, entries 7–8).[6d,8a,d,e] Unfortunately, the reaction with aliphatic terminal alkynes did not yield any product (Table 2, entries 22–23).[6d]

Based on the following observations and control experiments, a plausible mechanism is shown in Scheme 5.[8a,d,13,9b,10a,b,16] In one of our first observations during optimization of the reaction conditions, we noticed the formation of a white solid in the reaction, which was isolated from the reaction mixture *via* filtration, and on spectroscopic analysis it was found to be piperidinium chloride.

Hence, we can conclude that the formation of intermediate **I** is the initial step of the reaction. Thus, there are three plausible pathways for the metal-free three-component coupling to occur. The first proceeds *via* nucleophilic substitution of the halide by an alkyne (Path H); the second *via* nucleophilic



Scheme 5 The plausible mechanism for the three-component coupling to give propargylamines.

addition of an alkyne to an iminium ion (Path I); and the third *via* nucleophilic substitution of a methylene-bisamine by an alkyne (Path J). As it is well known that the reaction of a secondary amine with a dihalomethane affords either an electrophilic iminium ion **II** under acidic conditions or a bis-aminomethane intermediate **III** under basic conditions,[15] under the present acidic conditions the reactive species formed is probably either the iminium ion **II** or the halo-methyleneamine **I**, and not the bis-aminomethane **III**; therefore, the possibility of Path J is ruled out. Further, to confirm this we carried out a separate reaction with bis(dimethylamino)methane[17] and piperidine, and found that the dimethylamine-derived propargylamine was not formed in the reaction at all.

On the other hand, the possibility of Path I is also ruled out based on the observations of Vogel *et al*. that only a trace amount of propargylamine is formed *via* the reaction of an iminium ion **II** with alkynes under catalyst-free conditions.[4e] We confirmed this by the fact that no imine-derived propargylamine was formed in the presence of benzaldehyde under the optimized reaction conditions. As a result, the only plausible mechanism that could occur in the present protocol is Path H, *i.e.* the nucleophilic substitution of the halide by an alkyne; an example of such a nucleophilic substitution of a halogen atom with an adjacent substituent by PMe_3 was recently reported by Macgregor *et al*.[18] The formed carbocation **IV** on deprotonation affords the desired propargylamines. However, the mechanism presented here is preliminary and needs further investigation, which will be part of our research in the future.

Conclusions

In conclusion, we have developed a metal-free protocol for the synthesis of propargylamines *via* the three-component coupling of various dihalomethanes, alkynes, and secondary amines, affording moderate to good yields of the desired products. Metal-free conditions make the process highly economical and hence suitable for large-scale synthesis. The notable advantages of this methodology over the existing procedures are simplicity of operation, mild conditions, and high functional group tolerance.

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