Can the Crabbé Homologation Be Successfully Applied to the Synthesis of 1,3-Disubstituted Allenes?

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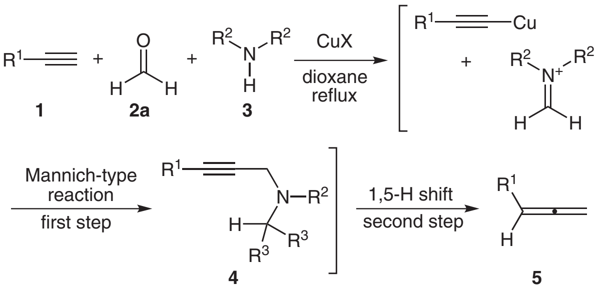
Abstract: The Crabbé homologation of terminal alkynes could be applied to the synthesis of 1,3-disubstituted allenes using aldehydes, *N*,*N*-dicyclohexylamine, and a catalytic amount of copper(I) iodide. The key to this success was the employment of an excess of aldehyde and amine, and performing the reaction under microwave irradiation conditions.

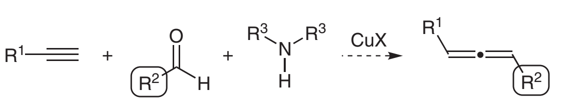
Key words: allenes, copper, microwave, multicomponent reaction, propargylamines

In the late 1970s, Crabbé and co-workers reported the copper(I) bromide mediated alkyne homologation to allenes by the reaction with formaldehyde (**2a**) and *N*,*N*-diisopropylamine (**3a**, $R^2 = i$-Pr) in refluxing dioxane (Equation 1).[1] While a variety of allene forming reactions have already been developed,[2] this traditional method is still widely used in the synthesis of monosubstituted allenes because of its simplicity, efficiency, versatility, and the use of an inexpensive copper salt. Recently, the improved Crabbé homologation was independently reported by two groups. Nakamura and co-workers found that the microwave (MW) irradiation accelerated the reaction,[3] whereas Ma and co-workers found that replacing **3a** and copper(I) bromide with *N*,*N*-dicyclohexylamine (**3b**, R^2 = Cy) and copper(I) iodide, respectively, led to an increase in the chemical yields of the allenes.[4]



Equation 1

The Crabbé homologation has long been believed not to be used for the synthesis of 1,3-disubstituted allenes (Scheme 1).[5,6] Alternatively, palladium,[7] gold,[8a] and silver[8b] recently emerged as useful transition metals for the transformation of propargylamines, a plausible intermediate of the Crabbé homologation, into the corresponding 1,3-disubstituted allenes. In addition, zinc was shown to promote the one-pot synthesis[6] of 1,3-disubstituted allenes by the reaction of alkynes with aldehydes in the presence of morpholine.[9] In this letter, we report our preliminary results that the copper-mediated alkyne homologation (Crabbé reaction) is still effective for the preparation of 1,3-disubstituted allenes under the modified conditions.



Scheme 1

The Crabbé homologation could be rationalized in terms of the intermediacy of the propargylamine intermediate (**4** in Equation 1), which should be formed by the Mannich-type reaction of copper acetylide with an iminium salt (first step). The second step involves the copper-mediated 1,5-hydride transfer to produce the allene **5**. The α-branched dialkylamine component, like *N*,*N*-dicyclohexylamine or *N*,*N*-diisopropylamine, is more suitable for this hydride shift than the di-*n*-alkylamines or unsubstituted cyclic amines. Copper salts, such as copper(I) bromide and copper(I) iodide, have already been found to be effective for the three-component coupling reactions of various aldehydes, alkynes, and amines (A^3 coupling) to produce the corresponding propargylamines, although the use of α-branched dialkylamines is prone to lead to slightly lower product yields.[7,10,11] Therefore, the first step in the Crabbé homologation using alkyl or aryl aldehydes would safely proceed under the influence of the copper catalyst. Thus, our initial investigation focused on the transformation of the propargylamines into the 1,3-disubstituted allenes by the copper-mediated 1,5-hydride transfer (second step in the Crabbé homologation), which has not yet been reported. *N*,*N*-Dicyclohexyl-8-phenyl-5-octyn-4-ylamine (**4ab**) was selected as a substrate and prepared by the A^3-coupling of 4-phenylbut-1-yne (**1a**), *n*-butyraldehyde (**2b**), and dicyclohexylamine (**3b**) under modified Knochel's conditions[11a] using 5 mol% of copper(I) bromide in refluxing toluene (**4ab**, 56%, allene **5ab**, 5% yield). However, the reaction of **4ab** with 1 equivalent of copper(I) bromide in refluxing dioxane (0.1 M) for 24 hours (almost

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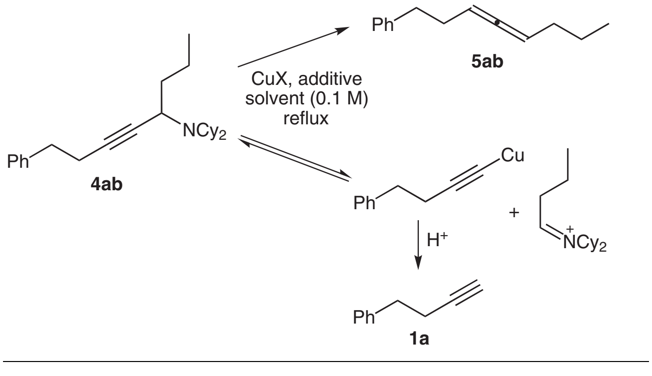
usual Crabbé conditions) gave the desired allene **5ab** only in 4% yield (Table 1, entry 1). When copper(I) iodide was used, the yield of the allene **5ab** increased to 10% (entry 2). Small amounts of the alkyne **1a** was observed in both reactions, indicating that the retro-Mannich reaction must have competitively occurred under the stated reaction conditions.[1d,12] Thus, the use of an aldehyde **2b** and amine **3b** as additives in order to suppress the retro-Mannich reaction was examined and actually found to improve the product yield (entry 3). Adding **2b** and **3b** might shift an equilibrium between propargylamine **4ab** and Csp–Csp^3-cleaved compounds to the direction that produce **4ab**, and accelerate the 1,5-hydride transfer. Further improvement in yield and reaction rate was realized by MW irradiation of the toluene solution. Thus, exposure of a mixture of propargylamine **4ab**, aldehyde **2b**, amine **3b**, and copper(I) iodide in the ratio of 1:3:3:0.1 in toluene to sealed-vessel MW irradiation conditions (200 °C, 3 h) led to a 68% yield of the allene (Table 1, entry 4). In addition to these conditions, the higher concentration (0.5 M) enabled us to reduce the amount of not only copper(I) iodide, but also the aldehyde and amine (Table 1, entry 5).

Table 1 Copper-Mediated Synthesis of **5ab** from **4ab**



Entry	CuX (equiv)	Additive (equiv)	Solvent	Time (h)	Yield of **5ab** (%)
1	CuBr (1)	–	dioxane	24[a]	4[b]
2	CuI (1)	–	dioxane	24[a]	10[b]
3	CuI (1)	**2b** (3) + **3b** (3)	dioxane	21	44
4[c]	CuI (0.1)	**2b** (3) + **3b** (3)	toluene	3[a]	68
5[c,d]	CuI (0.1)	**2b** (1) + **3b** (1)	toluene	2[a]	62

[a] Reaction did not go to completion.

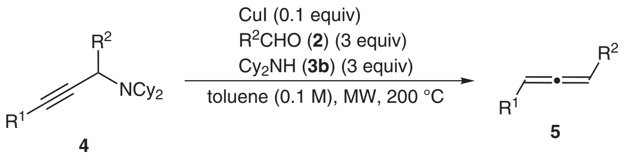
[b] Acetylene **1a** was detected on TLC.

[c] The reaction was performed under MW irradiation conditions at 200 °C.

[d] The reaction was performed in 0.5 M solution.

The conversion of various propargylamines into the corresponding allenes was next examined under the conditions in entry 4 (Table 1). The α-branched alkyl group on the propargylic position (R^2 group) slightly retarded the reaction, but did not influence the chemical yield (Table 2, entry 2). A shorter reaction time was achieved at the higher concentration (0.5 M, Table 2, entry 3). The siloxy functionality could be tolerated under these conditions (entry 6). The propargylamines with a phenyl group at R^1 and/or R^2 were not suitable substrates for this transformation (Table 2, entries 4, 7, and 8). When using **4ad** (R^2 = Ph) or **4db** (R^1 = Ph) as a substrate, the MW irradiation at temperatures lower than 200 °C resulted in a higher yield of the corresponding allene **5ad** or **5db**, indicating the instability of **4** or **5** under the reaction conditions at higher temperatures [Table 2, entries 4 and 7, cf. **5ad** (MW, 200 °C, 1 h, 16%) and **5db** (MW, 200 °C, 45 min, 12%)].

Table 2 Copper-Catalyzed Synthesis of **5** from **4**



Entry	4	R^1	R^2	Time (h)	Yield of **5** (%)
1	**4ab**	PhCH$_2$CH$_2$	*n*-Pr	3	**5ab** 68
2[a]	**4ac**	PhCH$_2$CH$_2$	*i*-Pr	5.5	**5ac** 67
3[a,b]	**4ac**	PhCH$_2$CH$_2$	*i*-Pr	2	**5ac** 69
4[b,c]	**4ad**	PhCH$_2$CH$_2$	Ph	3	**5ad** 32
5	**4bb**	Me(CH$_2$)$_5$	*n*-Pr	2	**5bb** 47
6	**4cb**	TBSO(CH$_2$)$_5$	*n*-Pr	4	**5cb** 62
7[a,b,d]	**4db**	Ph	*n*-Pr	2.5	**5db** 15
8[b,d]	**4dd**	Ph	Ph	3.5	**5dd** 2

[a] CuI (0.2 equiv) was used.

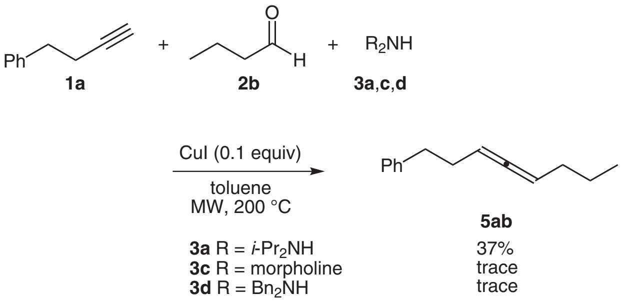
[b] The reaction was performed in 0.5 M solution.

[c] The reaction was performed at 150 °C.

[d] The reaction was performed at 165 °C.

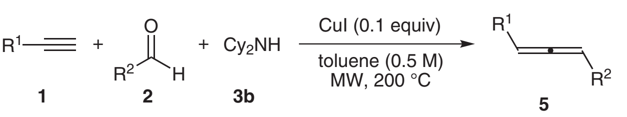
Having identified the conditions to convert propargylamines into allenes using a copper salt, we examined the one-pot allene formation reaction of an alkyne, aldehyde, and amine (Crabbé homologation). The exposure of a mixture of 4-phenylbut-1-yne (**1a**), *n*-butyraldehyde (**2b**), dicyclohexylamine (**3b**), and copper(I) iodide in the ratio of 1:1:1:0.1 in toluene (0.5 M) to the sealed-vessel MW irradiation conditions (200 °C, 2 h) led to the production of the allene **5ab** in 40% yield (Table 3, entry 1). An increase in the amount of **2b** and **3b** (each 1.5 equiv) improved the yield of **5ab** to 50% (Table 3, entry 2). When the reaction was conducted using 1 equivalent of copper(I) iodide under conventional heating for 15 hours, the desired **5ab** was obtained in 38% yield (Table 3, entry 3). Thus, the conditions shown in entry 2 (Table 3) were used for the formation of various 1,3-dialkyl-substituted allenes.[13] For the reaction of acetylenes **1a**–**c**, the product yields remained moderate to good with a slight decrease compared to the yields from the corresponding propargylamines, irrespective of the partner aldehyde (Table 3, entries 4–6). The respective slight increase in the amount of the aldehyde, amine, and copper(I) iodide improved the product yield in the case of entry 4 (**1a**/**2c**/**3b**/CuI = 1:2.3:1.8:0.2, 64% yield; cf. 1:1.5:1.5:0.1, 43% yield, Table 3). The acetylenes having a siloxy or tosylamido group at the propargylic position also reacted with aldehydes **2b** or **2c** to give the corresponding allenes in 35–64% yields (Table 3, entries 7–10). The reactions including phenylacetylene or benzaldehyde as the reaction component furnished the desired products in lower yields (Table 3, entries 11 and 12), which might be predictable based on the results shown in Table 2. The results of the reaction using other amines than dicyclohexylamine were in good agreement with the previously reported tendency in the original Crabbé reaction.[1,3,4] Thus, the use of diisopropylamine resulted in a lower yield of the allene, and both reactions using morpholine and dibenzylamine afforded only a trace amount of the desired product (Scheme 2).

In conclusion, we have shown that the transformation of propargylamines into 1,3-disubstituted allenes as well as the one-pot reaction from alkynes, aldehydes, and amines (Crabbé homologation) nicely proceeded by applying the MW irradiation conditions. The presence of excess aldehydes and amines versus the alkynes is crucial for the allene-forming reaction. The newly developed methods can provide allenes using only 0.1 or 0.2 equivalents of the inexpensive copper(I) iodide in high yields similar to the already reported methods,[6–8] especially when the propargylamines have aliphatic substituents on the acetylene terminus and the propargylic position.



Scheme 2 One-pot preparation of **5ab** using various amines **3**

Table 3 One-Pot Preparation of **5** from **1**, **2**, and **3b**[a]



Entry	1	R¹	2	R²	Time (h)	Yield of 5 (%)
1[b]	**1a**	$PhCH_2CH_2$	**2b**	*n*-Pr	2	**5ab** 40
2	**1a**	$PhCH_2CH_2$	**2b**	*n*-Pr	2	**5ab** 50
3[c]	**1a**	$PhCH_2CH_2$	**2b**	*n*-Pr	15	**5ab** 38
4[d,e]	**1a**	$PhCH_2CH_2$	**2c**	*i*-Pr	3.5	**5ac** 64
5	**1b**	$Me(CH_2)_5$	**2b**	*n*-Pr	2.5	**5bb** 43
6	**1c**	$TBSO(CH_2)_5$	**2b**	*n*-Pr	1.5	**5cb** 50
7	**1e**	$n\text{-}C_7H_{15}CH(OTBS)$	**2b**	*n*-Pr	2	**5eb** 60
8[d]	**1e**	$n\text{-}C_7H_{15}CH(OTBS)$	**2c**	*i*-Pr	3.5	**5ec** 61
9	**1f**	$n\text{-}C_7H_{15}CH(NHTs)$	**2b**	*n*-Pr	1	**5fb** 35
10[d,e]	**1f**	$n\text{-}C_7H_{15}CH(NHTs)$	**2c**	*i*-Pr	1.25	**5fc** 64
11[e,f]	**1a**	$PhCH_2CH_2$	**2d**	Ph	2.5	**5ad** 31
12[g]	**1d**	Ph	**2b**	*n*-Pr	5	**5db** 14

[a] Aldehyde **2** and amine **3b** (each 1.5 equiv) were used.
[b] Aldehyde **2b** and amine **3b** (each 1 equiv) were used.
[c] Reaction was performed using CuI (1 equiv) in refluxing toluene without MW heating.
[d] Aldehyde **2c** (2.3 equiv) and amine **3b** (1.8 equiv) were used.
[e] CuI (0.2 equiv) was used.
[f] The reaction was performed at 150 °C.
[g] The reaction was performed at 150 °C for 3 h and at 165 °C for 2 h.

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(13) **Typical Procedure for the Microwave-Assisted Crabbé Homologation**
Alkyne **1a** (65.0 mg, 0.500 mmol), aldehyde **2b** (68 μL, 0.75 mmol), amine **3b** (150 μL, 0.754 mmol), CuI (9.6 mg, 0.050 mmol), and toluene (1.0 mL) were mixed in a 2 mL process vial. The vial was sealed, and the reaction mixture was heated with microwaves to 200 °C for 2 h. After cooling, the mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel(hexane) to afford **5ab** (46.8 mg, 50%) as a colorless oil. IR ($CHCl_3$): 1961 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, TMS): $\delta = 7.27$ (t, $J = 7.6$ Hz, 2 H), 7.20–7.16 (m, 3 H), 5.14–5.06 (m, 2 H), 2.72 (t, $J = 7.6$ Hz, 2 H), 2.32–2.27 (m, 2 H), 1.97–1.87 (m, 2 H), 1.38 (sext, $J = 7.6$ Hz, 2 H), 0.90 (t, $J = 7.6$ Hz, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 204.1$, 141.9, 128.5, 128.2, 125.8, 91.3, 90.2, 35.5, 31.0, 30.7, 22.4, 13.6. MS (EI): *m/z* (%) = 186 (3.1) [M^+]. HRMS: *m/z* calcd for $C_{14}H_{18}$: 186.1409; found: 186.1407.