# The effects of amines on oxidative homo-coupling of terminal alkynes promoted by copper salts

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The effects of all kinds of amines on homo-couplings (Glaser reactions) of terminal alkynes promoted by copper salts and the Sonogashira coupling reactions were studied systematically. Diethylamine (2° amine) can serve as an excellent solvent, base and coordination ligand in the oxidative homo-coupling of terminal alkynes and several modified Glaser coupling procedures have been developed which are based on a catalytic amount of cuprous salts (CuI, CuBr or CuCl) with diethylamine systems. Homo-coupling of terminal acetylenes in the Sonogashira reaction could be inhibited by using triethylamine (3° amine) as reaction medium, and the cross-coupling products were formed as the exclusive products.

**Keywords:** Glaser reaction, Sonogashira coupling, copper salt, tuning of reactivity, amine

Homo-coupling of terminal alkynes is currently under intensive study.[1] Rigid and sterically undemanding di- and oligoacetylene moieties, which are frequently encountered in natural products,[2] are increasingly applied as key structural elements in synthetic receptors for molecular recognition.[3] Interesting electronic and optical properties of extensively π–conjugated systems have spurred research into new linear oligoalkynes, polyacetylenes and acetylenic carbon allotropes.[4] The synthetic challenges associated with these efforts have in turn spawned new methods.

In 1869, Glaser first discovered that terminal alkynes underwent oxidative self-coupling to form diacetylenes with CuCl in the presence of $NH_3{\cdot}H_2O$ and $O_2$.[5] Subsequently, Cameron observed the effect of substituting amines for ammonia in the catalyst mixture (CuCl–amine–amine•HCl–$O_2$).[6] Later, Eglinton and Calbraith found that copper(II) acetate in pyridine-methanol was an effective reagent for the oxidative coupling of acetylenes, but excess of the Cu(II) reagent was used because of the slow reaction.[7] In 1960, Hay noted that acetylenes could be coupled at room temperature with oxygen or air by using a catalytic amount of CuCl–pyridine complex.[8] Later, Hay continued his investigation on the oxidative coupling of acetylenes and noticed that a bidentate tertiary amine ligand *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) with CuCl is a good complex catalyst for the Glaser reaction.[9] In the last three decades, a variety of copper salt–amine systems, such as $Cu(OAc)_2$–pyridine,[10] CuCl–TMEDA,[11] $CuCl_2$–CuCl–pyridine,[12,3c] CuCl–TMEDA–pyridine,[13] CuCl(OH)–TMEDA,[14] CuCl–$Cu(OAc)_2$–pyridine,[15] CuI–TMEDA[16] and CuI–pyrrolidine[17] were recommended for this transformation. Recently, the use of palladium(0) complexes was invoked and optimised to obtain terminal acetylene bicoupling products as the major ones.[18] However, Cu-salts-promoted methods suffer from moderate yields, long reaction times, and excess of copper salts used in most of the reactions. We therefore made a systematic investigation of the homo-coupling of terminal alkynes promoted by various copper salts in various organic amines as presented below.

## Results and discussion

*Glaser coupling reaction using various copper salts and amines*

Using the classic Glaser reaction protocol, we examined the reaction with a different amine and a variety of copper salts. The results are listed in Table 1. Phenylacetylene was chosen as a model compound for this investigation. As is evident from Table 1, the acetylenic homo-coupling product was formed exclusively at room temperature when the reaction was carried out in diethylamine, *n*-butylamine, piperidine, cyclohexylamine, pyridine and TMEDA, which served as the base, solvent and coordination ligand. No self-coupling compound was observed when the reaction was performed in triethylamine, aniline, and triethanolamine at ambient temperature, as well as at reflux. About 10% yield of homo-coupling product was obtained when the reaction was run in dibenzylamine. Among the efficient copper salt–amine systems, the cuprous salt–amine system was more effective than the cupric salt–amine one. An interesting finding was that primary aliphatic amines, such as *n*-butylamine, cyclohexylamine, and secondary amine (diethylamine, piperidine), could serve as an excellent reaction media for the homo-coupling of terminal alkynes. However, primary aromatic amine (aniline) inhibited the reaction because of its weak basicity, poor coordination, and the property of easily being oxidised by copper salt and dioxygen. Due to the steric effect, dibenzylamine only gave a low yield of the self-coupling product. No homo-coupling product was generated when the reaction was carried out in tertiary aliphatic amines (triethylamine and triethanolamine, except for TMEDA), and a moderate-to-good yield of diacetylene was provided when the reaction was performed in pyridine. It is noteworthy that a good-to-excellent yield of diacetylene was formed when the reaction was carried out in TMEDA possibly the result of its good (bidentate) coordination.

In addition, (Table 1), an addition of acetone could increase the homocoupling yield of terminal alkynes significantly in the CuBr–TMEDA, CuCl–TMEDA and $CuCl_2$–TMEDA reaction systems. Possibly this was due to the improved solubility of these catalysts in acetone.[16] The above unexpected results lead us to believe that the reaction medium plays a very important role in this reaction.

Based on the known studies of the mechanism for Glaser-type homo-coupling reactions,[5, 19] we suggest that the phenylacetylene reacted first with cuprous salt to form a copper(I) phenylacetylide, which then underwent smooth oxidative dimerisation in air to give diphenyldiacetylene.

*The Glaser coupling reaction of terminal alkynes with cuprous salt–amine reaction system*

The recommended new and easily available cuprous salt–amine reaction systems, such as CuI (cat.)–diethylamine, CuBr (cat.)–diethylamine, CuCl (cat.)–diethylamine and CuCl (cat.)–*n*-butylamine have been used for the Glaser

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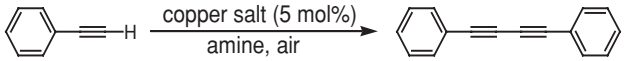
**Table 1** Glaser coupling reaction using various copper salts and amines[a]




| Amines | CuI Yield/%[b] | CuBr Yield/%[b] | CuCl Yield/%[b] | $CuCl_2$ Yield/%[b] | $CuSO_4$ Yield/%[b] | $Cu(OAc)_2$ Yield/%[b] |
|---|---|---|---|---|---|---|
| $n$-$C_4H_9NH_2$ | 87 | 94 | 99 | 57 | 58 | 51 |
| $c$-$C_6H_{11}NH_2$ | 85 | 79 | 78 | 83 | 70 | 75 |
| $C_6H_5NH_2$ | 0, trace[c] | 0 | 0 | 0 | 0 | 0 |
| $(C_2H_5)_2NH$ | 98 | 97 | 98 | 72 | 73 | 69, 99[d] |
|  | 83 | 86 | 95 | 78 | 71 | 64 |
| $(C_6H_5CH_2)_2NH$ | 11, 13[c] | 9 | 11 | 8 | 10 | 12 |
| $(C_2H_5)_3N$ | 0, trace[c] | 0 | 0 | 0 | 0 | 0 |
| $(HOCH_2CH_2)_3N$ | 0, trace[c] | 0 | 0 | 0 | 0 | 0 |
| $[(CH_3)_2N]_2(CH_2)_2$ | 99, 99[e] | 57, 71[e] | 75, 96[e] | 75, 90[e] | 65 | 71 |
|  | 31, 51[c] | 82 | 91 | 26 | 19 | 43, 83[c] |

[a]Reactions were run with phenylacetylene (1.0 mmol), copper salt (0.05 mmol), amine (2 ml) at room temperature for 3 h under air and their progress was monitored by TLC. [b]Isolated yield (average of three runs). [c]Reactions were carried out with phenylacetylene (1.0 mmol), copper salt (0.05 mmol), amine (2 ml) at 80–90 °C for 3 h. [d]Reactions were conducted with phenylacetylene (1.0 mmol), $Cu(OAc)_2$ (0.05 mmol), diethylamine (0.05 mmol), acetone (5 ml) at ambient temperature for 3 h under air. [e]Reactions were performed with phenylacetylene (1.0 mmol), CuX or $CuCl_2$ (0.05 mmol), TMEDA (0.10 mmol), acetone (5 ml) at ambient temperature for 3 h under air.

coupling reaction on a variety of terminal alkynes. The results are summarised in Table 2. Phenylacetylene, *p*-methylphenylacetylene, 1-decyne, 1-octyne and propargyl alcohol underwent homo-coupling reaction smoothly in diethylamine or *n*-butylamine, to generate the corresponding 1,4-disubstituted-1,3-butadiyne with excellent-to-quantitative yields in the presence of catalytic amount of cuprous halides (5% CuI, 5% CuBr or 5% CuCl respectively). The reaction was carried out simply by stirring terminal alkynes with commercially available cuprous halides in amines under an air atmosphere without bubbling pure oxygen into the solution (up to 10 mmol reaction scale). These methods provide alternative routes to synthesise symmetrically disubstituted 1,3-butadiyne.

*Sonogashira coupling reaction of terminal alkynes and aryl halides with diminished homocoupling in triethylamine. Tuning of reactivity towards Glaser or Sonogashira coupling depending on the reaction medium*

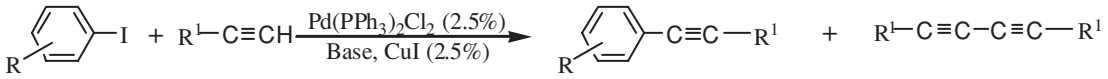
The Sonogashira coupling reaction of terminal alkynes and aryl or alkenyl halides is a versatile and efficient route to terminal and internal alkynes.[20] Numerous applications to natural products, nonlinear optical materials, and carbohydrate sensing and molecular electronics syntheses have been reported by using Sonogashira coupling.[21] In general, the reaction conditions are mild, and many reactions can be performed at ambient temperature. However, the Sonogashira reaction often generates homo-coupling products of terminal alkynes (Glaser coupling or Hay coupling) along with the main reaction in considerable yields under standard reaction conditions. These undesirable by-products are generally not easily separated from the desired products. Although a number of modifications have been used to obtain symmetrical or unsymmetrical butadiynes,[22] little attention has been paid to diminishing acetylenic self-coupling and enhancing the desired Sonogashira cross-coupling.[23]

Based on the significant difference of homo-coupling reactions of terminal alkynes in diethylamine and triethylamine, we carried out the classic Sonogashira reaction in these solvents. Although there is no systematic difference between the total yields from any of the reactions carried out in the presence of $N_2$ or in the presence of $O_2$, in fact a competition between homo-coupling and cross-coupling reactions was observed and the yields of the homo-coupling (Glaser reaction) and cross-coupling (Sonogashira reaction) products have been found to be drastically different in diethylamine or triethylamine (Scheme 1). The Sonogashira reaction can be carried out by using triethylamine as base, as well as solvent, to diminish the homo-coupling side reaction and improve the cross-coupling. The results are presented in Scheme 1. The ratios of the cross-coupling to homo-coupling products were found to be in the range of 73/27 to 80/20 when the Sonogashira reactions of phenylacetylene with *p*-iodoanisole were carried out in triethylamine.[24] However, the ratios of the cross-coupling to homo-coupling products were found to be from 57/43 to 49/51 when the corresponding reactions were performed in diethylamine. When the reactions of 1-decyne with *p*-iodoanisole were run in triethylamine, the exclusive cross-coupling products were obtained, and when the corresponding reactions were carried out in diethylamine, 15–20 % yields of homo-coupling by-products were generated. This result indicates that the reaction medium can serve as an important factor for the chemoselectivity between homo-

**Table 2** Glaser coupling reaction of terminal alkynes with cuprous salt–amine system [a]

| Terminal alkynes | CuI/DEA Yield/%[b] | CuBr/DEA Yield/%[b] | CuCl/DEA Yield/%[b] | CuCl/*n*-butylamine Yield/%[b] |
|---|---|---|---|---|
| $C_6H_5C{\equiv}CH$ | 98 | 97 | 98 | 99 |
| $p$-$CH_3C_6H_4C{\equiv}CH$ | 95 | 96 | 97 | 96 |
| $n$-$C_6H_{13}C{\equiv}CH$ | 90 | 92 | 91 | 92 |
| $n$-$C_8H_{17}C{\equiv}CH$ | 93 | 94 | 92 | 93 |
| $HC{\equiv}CCH_2OH$ | 90 | 91 | 94 | 92 |

[a]The reactions were performed with terminal alkyne (5.0 mmol), cuprous salt (0.25 mmol), amine (10 ml) at room temperature for 3 h under air and their progress was monitored by TLC. DEA is an abbreviation of diethylamine. [b]Isolated yield (average of three runs).




| | | |
|---|---|---|
| R = *p*-$CH_3O$, $R^1$= $C_6H_5$, | Base = triethylamine, $N_2$ | Total yield* 82% (80/20) |
| R = *p*-$CH_3O$, $R^1$= $C_6H_5$, | Base = triethylamine, $O_2$ | Total yield 88% (73/27) |
| R = *p*-$CH_3O$, $R^1$= $C_6H_5$, | Base = diethylamine, $N_2$ | Total yield 92% (57/43) |
| R = *p*-$CH_3O$, $R^1$= $C_6H_5$, | Base = diethylamine, $O_2$ | Total yield 95% (49/51) |
| R = *p*-$CH_3O$, $R^1$= *n*-$C_8H_{17}$, | Base = triethylamine, $N_2$ | Total yield 92% (100/0) |
| R = *p*-$CH_3O$, $R^1$= *n*-$C_8H_{17}$, | Base = triethylamine, $O_2$ | Total yield 89% (100/0) |
| R = *p*-$CH_3O$, $R^1$= *n*-$C_8H_{17}$, | Base = diethylamine, $N_2$ | Total yield 95% (85/15) |
| R = *p*-$CH_3O$, $R^1$= *n*-$C_8H_{17}$, | Base = diethylamine, $O_2$ | Total yield 93% (80/20) |
| R = *p*-$CH_3CO$, $R^1$= $C_6H_5$, | Base = triethylamine, $N_2$ | Total yield 92% (77/23) |
| R = *p*-$CH_3CO$, $R^1$= $C_6H_5$, | Base = triethylamine, $O_2$ | Total yield 90% (70/30) |
| R = *p*-$CH_3CO$, $R^1$= $C_6H_5$, | Base = diethylamine, $N_2$ | Total yield 92% (31/69) |
| R = *p*-$CH_3CO$, $R^1$= $C_6H_5$, | Base = diethylamine, $O_2$ | Total yield 97% (23/77) |
| R = *p*-$CH_3CO$, $R^1$= *n*-$C_8H_{17}$, | Base = triethylamine, $N_2$ | Total yield 94% (100/0) |
| R = *p*-$CH_3CO$, $R^1$= *n*-$C_8H_{17}$, | Base = triethylamine, $O_2$ | Total yield 99% (100/0) |
| R = *p*-$CH_3CO$, $R^1$= *n*-$C_8H_{17}$, | Base = diethylamine, $N_2$ | Total yield 99% (80/20) |
| R = *p*-$CH_3CO$, $R^1$= *n*-$C_8H_{17}$, | Base = diethylamine, $O_2$ | Total yield 93% (78/22) |

*Total yield represents the percentage of acetylene going to either Sonogashira or Glaser product and isolated yield (average of three runs).

**Scheme 1** Tuning of reactivity towards Glaser or Sonogashira coupling depending on amine.

coupling of terminal alkynes and cross-coupling reaction of terminal alkynes with organic halides. However, the exact role of triethylamine and diethylamine in the reaction is not fully clear. Further investigation is currently underway and will be reported in due course.

## Conclusions

The remarkable solvent, coordination and base effects of amines on oxidative homo-coupling of terminal alkynes promoted by copper salts have been explored. We have found that easily available diethylamine can serve as an excellent solvent, base and coordination ligand in the oxidative homo-coupling of terminal alkynes. Several modified Glaser coupling reaction procedures have been developed by using CuI (cat.)-diethylamine, CuBr (cat.)-diethylamine, CuCl (cat.)-diethylamine, and CuCl (cat.)-*n*-butylamine reaction systems. Homo-coupling of terminal acetylenes in the Sonogashira reaction can be diminished by using triethylamine as reaction medium and the cross-coupling product was formed as the exclusive product.

## Experimental

*Physical measurements and materials*

Melting points were recorded on a melting point apparatus and are uncorrected. All $^1H$ and $^{13}C$ NMR spectra were recorded at 400 or 250 MHz, and 100 or 62.5 MHz respectively. Chemical shifts are given as δ values with reference to tetramethylsilane (TMS) as internal standard. IR spectra were obtained by using a Nicolet NEXUS 470 spectrophotometer. UV spectra were recorded on a TU-1901 UV/VIS spectrophotometer. The Chemicals were purchased from commercial suppliers and were used without purification prior to use. Products were purified by flash column chromatography.

*General procedure for Glaser coupling*

Terminal alkyne (1.00 mmol) was added with stirring to a mixture of copper salt (1.00 mmol) and amine (2 ml) in a round-bottomed flask. The mixture was stirred at room temperature in the open air and the reaction progress was monitored by TLC. After the reaction was completed (about 3 h), the reaction mixture was acidified with diluted hydrochloric acid (0.2 mol/l, 1 ml). Diethyl ether (10 ml × 2) was added to extract the products. After the organic layer was dried with anhydrous sodium sulfate, the solvents were evaporated under reduced pressure. The product was purified by flash chromatography to yield the corresponding homo-coupling product.

*Typical procedure for Sonogashira reaction*

CuI (0.05 mmol) was added to a mixture of $[PdCl_2(PPh_3)_2]$ (0.05 mmol) and an $Et_3N$ solution (5 ml) of aromatic halide (2 mmol) under an $N_2$ atmosphere in a flask equipped with a magnetic stirrer bar. Terminal alkyne (2 mmol) in $Et_3N$ (2 ml) solution was added dropwise over 0.5–1 h. After the reaction was carried out at room temperature for 6 h, $Et_3N$ was removed under reduced pressure. Water was added to the residue. The mixture was extracted with ether (3 × 20 ml). After the organic layer was dried ($Na_2SO_4$), the solvent was removed under reduced pressure. The product was separated by column chromatography using silica gel to generate the corresponding cross-coupling product.

*1,4-Diphenyl-1,3-butadiyne*: M.p. 87–88°C (lit.[25] 88°C); UV (hexane) λ: 328, 307, 289 nm; IR (KBr) ν: 2147 $cm^{-1}$ (C≡C); $^1H$ NMR ($CDCl_3$) δ 7.52–7.49 (m, 2 × 2H), 7.34–7.27 (m, 2 × 3H); $^{13}C$ NMR ($CDCl_3$) δ 132.4, 129.2, 128.4, 121.7, 81.6, 74.0.

*1,4-Bis(4-methylphenyl)-1,3-butadiyne*: M.p. 182–184°C (lit.[25] 183°C); IR (KBr) ν: 2142 $cm^{-1}$ (C≡C); $^1H$ NMR ($CDCl_3$) δ 7.41 (d, *J* = 8.0 Hz, 2 × 2H), 7.12 (d, *J* = 7.9 Hz, 2 × 2H), 2.35 (s, 2 × 3H); $^{13}C$ NMR ($CDCl_3$) δ 139.5, 132.4, 129.2, 118.8, 81.6, 73.5, 21.6.

*7,9-Hexadecadiyne*: Oil;[26] IR (film) ν: 2125 $cm^{-1}$ (C≡C); $^1H$ NMR ($CDCl_3$) δ 2.24 (t, *J* = 6.9 Hz, 2 × 2H), 1.57–1.26 (m, 2 × 8H), 0.89 (t, *J* = 6.7 Hz, 2 × 3H); $^{13}C$ NMR ($CDCl_3$) δ 77.4, 65.3, 31.3, 28.5, 28.3, 22.5, 19.2, 14.0.

*9,11-Eicosdiyne* Oil:[27] IR (film) ν: 2129 $cm^{-1}$ (C≡C); $^1H$ NMR ($CDCl_3$) δ 2.23 (t, *J* = 6.8 Hz, 2 × 2H), 1.57–1.27 (m, 2 × 12H), 0.88 (t, *J* = 6.3 Hz, 2 × 3H); $^{13}C$ NMR ($CDCl_3$) δ 77.5, 65.3, 31.8, 29.1, 29.0, 28.8, 28.4, 22.6, 19.1, 14.0; MS (70 eV) *m/z* (%): 254 ($M^+$–$C_2H_5$, 2), 217 (5), 175 (8), 161 (16), 147 (24), 133 (29), 119 (42), 105 (56), 91 (100).

*2,4-Hexadiyne-1,6-diol*: White solid; m.p. 113–115°C (lit.[28] 113–114 °C); $^1H$ NMR ($CD_3COCD_3$) δ 4.41 (br, 2H), 4.25 (s, 4H); $^{13}C$ NMR ($CD_3COCD_3$) δ 78.7, 69.4, 50.9.

*1-(4-Acetylphenyl)phenylacetylene*: M.p. 95–97 °C (lit.[29] 95–96 °C); $^1H$ NMR ($CDCl_3$) δ 7.92 (d, *J* = 8.44 Hz, 2H), 7.60 (d, *J* = 8.41 Hz, 2H), 7.54–7.52 (m, 2H), 7.37–7.35 (m, 3H), 2.60 (s, 3H); $^{13}C$ NMR ($CDCl_3$) δ 197.1, 136.0, 131.7, 131.6, 128.6, 128.4, 128.2, 128.1, 122.7, 92.6, 88.7, 26.5; MS *m/z* (%) 220 ($M^+$, 62), 205 (100), 176 (51), 151 (21), 102 (11), 88 (22).

*1-(4-Methoxylphenyl)-1-decyne*: Oil;[30].$^1H$ NMR ($CDCl_3$) δ 7.31 (d, *J* = 8.74 Hz, 2H), 6.90 (d, *J* =8.75 Hz, 2H), 3.76 (s, 3H), 2.34 (t, *J* = 7.05 Hz, 2H), 1.65–1.57 (m, 2H), 1.45–1.27 (m, 10 H), 0.88 (t, *J* = 6.08 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 159.1, 132.9, 116.4, 113.9, 88.8, 80.2, 55.2, 31.8, 29.2, 29.1, 28.9, 22.2, 19.4, 14.1; MS *m/z* (%) 244 ($M^+$, 19), 201 (5), 188 (24), 173 (30), 159 (31), 147 (100), 121 (35), 115 (20), 91 (14).

*1-(4-Acetylphenyl)-1-decyne*: Oil; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 7.85 (m, 2H), 7.37 (m, 2H), 2.55 (s, 3H), 2.42 (t, *J* = 7.21 Hz, 2H), 1.61–1.59 (m, 2H), 1.44–1.42 (m, 2H), 1.34–1.29 (m, 8H), 0.89 (t, *J* = 5.21 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 197.2, 135.7, 131.7, 129.2, 128.2, 94.4, 80.2, 31.9, 29.2, 29.1, 29.0, 28.6, 26.5, 22.7, 19.6, 14.1. Anal. Calcd for $C_{18}H_{24}O$: C, 84.3; H, 9.4. Found: C, 84.5; H, 9.4. HRMS (EI) calcd for $C_{18}H_{24}O$ 256.1827, found: 256.1836.

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