

Glaser Coupling Reaction without Organic Solvents and Bases under Near-critical Water Conditions

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A Glaser coupling reaction of terminal alkynes in the presence of cupric chloride without organic solvents and bases under near-critical water has been developed.

Keywords Glaser coupling reaction, terminal alkyne, cupric chloride, near-critical water, 1,3-diyne

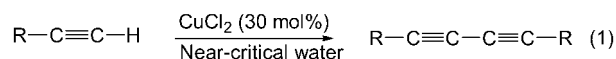
Introduction

1,3-Diynes are very important intermediates and target molecules in biological, polymer and material science.¹⁻⁴ A classical, effective and useful method for preparing diacetylenes was discovered by Carl Glaser in 1869, which involves a cuprous salt (CuCl) promoted oxidative homo-coupling reaction of terminal alkynes in the presence of oxygen, ammonia and ammonium chloride.⁵ Subsequent studies indicate that a variety of copper salts (including cuprous and cupric salts, generally used in a stoichiometric amount) are effective mediators for the coupling reaction. These reactions are generally carried out in organic solvents such as methanol, acetone, pyridine, methyl cellosolve, benzene and toluene.⁶⁻¹² The solvents often pose waste-disposal-related problems. In addition, amines, such as piperidine, pyridine, diethylamine, triethylamine and *N,N,N',N'*-tetramethylethylenediamine are required in most Glaser reaction and they have an offensive smell and add to the environmental complications. We have recently reported an energy-efficient modification of the Glaser coupling by using cupric chloride doped on the mixture of potassium fluoride and alumina under solventless reaction conditions.¹³

Organic reactions in aqueous solution have received much attention in recent years.^{14,15} Unfortunately most organic compounds are poorly soluble in water at ambient temperature. Nonetheless, the remarkable properties of water near its critical point ($t_c=374\text{ }^\circ\text{C}$, $p_c=2.21\times 10^7\text{ Pa}$) have promoted researchers to use it instead of organic solvents in organic synthesis. As temperature increases, water becomes more compatible as a medium for reaction of organic.¹⁶⁻¹⁹ There have been an increasing number of papers in which it is suggested that near-critical water is used as excellent solvent for

organic reactions because organic reactions in near-critical water offer many advantages over those in traditional organic solvents.²⁰⁻²³

Here, we wish to report a Glaser coupling reaction of terminal alkyne in the presence of cupric chloride (30 mol%) without organic solvents and bases under near-critical water conditions. The reaction affords the corresponding coupling products in good yields [Eq. (1)].



Results and discussion

Optimization reaction conditions for Glaser coupling in water

Our investigation began with an effort to optimize reaction conditions for the oxidative coupling of terminal alkyne using transition-metal salt in near-critical water. Phenylacetylene was chosen as a model compound for the optimization process. The results are summarized in Table 1.

As can be seen from Table 1, the reaction temperature played an important role in the oxidative homo-coupling reaction of terminal alkynes. It is evident that phenylacetylene could not be completely oxidized and subsequently coupled to form diphenyldiacetylene without organic solvents and bases in the presence of cupric chloride in water at less than 170 °C (Entry 6, Table 1), and only a moderate yield of diphenyldiacetylene was obtained at 250 °C because of the polymerization (Entry 1, Table 1). A good yield of product was obtained at temperature range of 190—230 °C. The Glaser coupling reaction requires a copper salt

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Received May 29, 2003; revised September 19, 2003; accepted October 20, 2003.

Project supported by the National Natural Science Foundation of China (Nos. 20372024, 20172018), the Excellent Scientist Foundation of Anhui Province (No. 2001040), the Natural Science Foundation of the Education Department of Anhui Province (No. 2002kj254zd), the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry (No 2002247) and the Excellent Young Teachers Program of Ministry of Education (No. 2024), China.

Table 1 Optimization reaction conditions for Glaser coupling of phenylacetylene in hot water^a

$\text{R}-\text{C}\equiv\text{C}-\text{H} \xrightarrow[\text{Hot water}]{\text{Metal salt}} \text{R}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{R}$					
Entry	Metal salt	Amount of metal salt/mmol	Temp./°C	Time/h	Yield ^b /%
1	CuCl ₂	0.30	250	2	58
2	CuCl ₂	0.30	230	2	67
3	CuCl ₂	0.30	210	2	74
4	CuCl ₂	0.30	200	2	78
5	CuCl ₂	0.30	190	2	75
6	CuCl ₂	0.30	170	2	68
7	CuCl ₂	0	200	2	Trace
8	CuCl ₂	0.10	200	2	61
9	CuCl ₂	0.20	200	2	77
10	CuCl ₂	0.50	200	2	78
11	CuSO ₄	0.30	200	2	72
12	Cu(OAc) ₂	0.30	200	2	54
13	ZnSO ₄	0.30	200	2	Trace
14	ZnCl ₂	0.30	200	2	Trace
15	CuCl	0.30	200	2	66
16	CuCl ₂	0.30	200	1	68
17	CuCl ₂	0.30	200	3	73
18	CuCl ₂	0.30	200	5	71
19	CuCl ₂ ^c	0.30	200	2	75
20	CuCl ₂ ^d	0.30	200	2	72

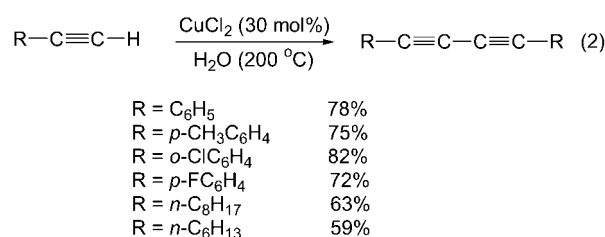
^a Reaction conditions: phenylacetylene (1 mmol), transition metal salt (0.30 mmol), tap water (10 mL) in a high *T/p* batch reactor system. ^b Isolated yields. ^c In the presence of NaOAc (2 mmol). ^d In the presence of Na₂CO₃ (2 mmol).

to promote the reaction. The efficiency of the transition metal salt decreases in the following order: CuCl₂ > CuSO₄ > CuCl > Cu(OAc)₂ >> ZnSO₄ ≈ ZnCl₂. The ratio of cupric chloride to phenylacetylene was also examined. The results showed that when the ratio of cupric chloride to phenylacetylene was less than 0.1 : 1, the reaction was not completed (Entries 7 and 8, Table 1), while the ratio equaled or was more than 0.2 : 1, satisfactory results were obtained (Entries 4, 9 and 10, Table 1). The effect of reaction time on the Glaser coupling of phenylacetylene was explored and the results indicated that the reaction was not completed when the reaction time was less than 1 h (Entry 16, Table 1). However, no increase of yield was observed when reaction time was prolonged. Surprisingly, the isolated yield of Glaser coupling product was not increased when the reaction was carried out in the presence of bases under near-critical water conditions (Entries 19 and 20, Table 1). The optimization reaction conditions for the oxidative coupling of phenylacetylene were found to be CuCl₂ (0.3 mmol), phenylacetylene (1 mmol), H₂O (10

mL) at 200 °C for 2 h without organic solvents and bases.

Glaser coupling reaction without organic solvents and bases in near-critical water

A variety of terminal alkynes were successfully coupled using the optimized reaction conditions. The results are listed in Eq. (2). In the presence of cupric chloride (30 mol%) without organic solvents and bases under near-critical water reaction conditions, homo-coupling of terminal alkyne occurred smoothly to produce the desired diacetylene in a moderate to good yield. Substituent effect was also examined. The results indicated that the reaction is relatively insensitive to the electronic nature (electron-donating and electron-withdrawing) of substituents on the aromatic rings.



Although the detailed reaction mechanism is not clear, the reaction presumably proceeded through the Cu(II)-promoted oxidation of terminal alkyne followed by self-coupling sequence reaction procedure. Further investigation is currently underway in our laboratory and will be reported in due course.

Conclusion

A reliable and practical procedure for the synthesis of diacetylenes via a Glaser coupling reaction was developed which involved the use of cupric chloride (30 mol%) in near-critical water (200 °C) without organic solvents and bases.

Experimental

Melting points were recorded on a WRS-1A melting point apparatus and are uncorrected. All ¹H NMR spectra were recorded on a 250 MHz Bruker AC 250 FT-NMR spectrometer. Chemical shifts are given as δ value with reference to tetramethylsilane (TMS) as internal standard. IR spectra were obtained by using a Nicolet NEXUS 470 spectrophotometer. GC/MS data were obtained by using a Hewlett-Packard 6890 series GC equipped with a 5983 mass selective detector. The reagents were received from commercial supply without purification prior to use. Products were purified by flash column chromatography.

General procedure of Glaser coupling reaction in the presence of cupric chloride in water

Terminal alkyne (1.00 mmol) and cupric chloride (40 mg, 0.3 mmol) were added to a high temperature and

pressure stainless steel autoclave reactor charged with tap water (10 mL) with stirring. The reactor was heated at 200 °C for 2 h. After cooling, ether (10 mL × 2) was added to extract the products. The organic layer was dried over anhydrous sodium sulfate and the solvents were evaporated under reduced pressure. The product was purified by flash chromatography to yield diacetylene.

1,4-Diphenyl-1,3-butadiyne m.p. 87—88 °C (lit.²⁴ 88 °C); ¹H NMR (CDCl₃) δ: 7.52—7.49 (m, 4H), 7.34—7.27 (m, 6H); ¹³C NMR (CDCl₃) δ: 132.4, 129.2, 128.4, 121.7, 81.6, 74.0; IR (KBr) ν: 2147 (C≡C) cm⁻¹.

1,4-Bis(4-methylphenyl)-1,3-butadiyne m.p. 182—184 °C (lit.²⁴ 183 °C); ¹H NMR (CDCl₃) δ: 7.41 (d, *J*=8.0 Hz, 4H), 7.12 (d, *J*=7.9 Hz, 4H), 2.35 (s, 6H); ¹³C NMR (CDCl₃) δ: 139.5, 132.4, 129.2, 118.8, 81.6, 73.5, 21.6; IR (KBr) ν: 2142 (C≡C) cm⁻¹.

1,4-Bis(2-chlorophenyl)-1,3-butadiyne m.p. 138—140 °C (lit.²⁵ 139.5—140 °C); ¹H NMR (CDCl₃) δ: 7.58—7.55 (m, 2H), 7.43—7.39 (m, 2H), 7.34—7.20 (m, 4H); ¹³C NMR (CDCl₃) δ: 137.0, 134.4, 130.3, 129.4, 126.6, 121.8, 79.4, 78.4; IR (KBr) ν: 2138 (C≡C) cm⁻¹.

1,4-Bis(4-fluorophenyl)-1,3-butadiyne m.p. 196—198 °C (lit.³ 195—197 °C); ¹H NMR (CDCl₃) δ: 7.52—7.48 (m, 4H), 7.07—7.00 (t, *J*=8.7 Hz, 4H); ¹³C NMR (CDCl₃) δ: 163.1 (d, *J*=250.0 Hz), 134.5 (d, *J*=8.3 Hz), 117.8, 115.9 (d, *J*=22.5 Hz), 80.43, 73.54; IR (KBr) ν: 2152 (C≡C) cm⁻¹.

7,9-Hexadecadiyne Oil²⁶; ¹H NMR (CDCl₃) δ: 2.24 (t, *J*=6.9 Hz, 4H), 1.57—1.26 (m, 16H), 0.89 (t, *J*=6.7 Hz, 6H); ¹³C NMR (CDCl₃) δ: 77.4, 65.3, 31.3, 28.5, 28.3, 22.5, 19.2, 14.0; IR (film) ν: 2125 (C≡C) cm⁻¹.

9,11-Eicosdiyne Oil²⁷; ¹H NMR (CDCl₃) δ: 2.23 (t, *J*=6.8 Hz, 4H), 1.57—1.27 (m, 24H), 0.88 (t, *J*=6.3 Hz, 6H); ¹³C NMR (CDCl₃) 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⁺—C₂H₅, 2), 217 (5), 175 (8), 161 (16), 147 (24), 133 (29), 119 (42), 105 (56), 91 (100); IR (film) ν: 2129 (C≡C) cm⁻¹.

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