

Glaser coupling reaction in supercritical carbon dioxide

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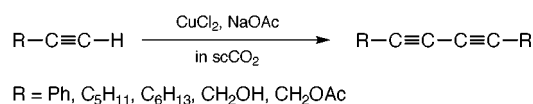
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It is demonstrated for the first time that Glaser coupling can be carried out smoothly in supercritical carbon dioxide using a solid base (NaOAc) instead of amines.

Considerable attention has recently been focused on using supercritical carbon dioxide (scCO₂) as a medium for organic reactions.^{1–3} As a solvent the attractive physical and toxicological properties of scCO₂ have made it superior to conventional organic solvents with regard to environmental considerations.

Diacetylenes are central to many biological and polymer molecules.^{4–8} Many of the most useful methods for the synthesis of diacetylenes^{8–10} involve cupric salt promoted coupling reactions, Glaser first observed that terminal acetylenes underwent oxidative coupling to diacetylenes with CuCl in the presence of NH₄OH. Subsequent studies have shown that a variety of cupric salts or oxygen in the presence of cuprous salts can be employed. The oxidation has the further advantage of solvent versatility. Water, methanol, Methyl Cellosolve, acetone, pyridine, cyclohexylamine and toluene have all been used as solvents for the reaction with nearly equal success. Amines, most frequently pyridine and tetramethylenediamine, are required in almost all Cu^{II}-promoted Glaser coupling. However, amines often have unpleasant smells and flavors. The present study is the first demonstration that Glaser coupling can be carried out in the presence of CuCl₂ in scCO₂ using NaOAc instead of amines (Scheme 1).



Scheme 1

Our investigation began with an effort to optimize reaction conditions for the oxidative coupling of terminal acetylenes using CuCl₂ and NaOAc. Phenylacetylene was chosen as a model substrate for the optimization process (entries 1–8, Table 1). The final optimized reaction conditions for Glaser coupling

Table 1 Oxidation coupling of terminal acetylenes in scCO₂^a

Run	Alkyne	Base	t/h	Conv. (%) ^b	Isolated yield (%)
1 ^c	PhC≡CH	NaOAc	4	12	10
2 ^d	PhC≡CH	NaOAc	4	81	39
3	PhC≡CH	none	4	63	50
4	PhC≡CH	pyridine	4	50	44
5 ^e	PhC≡CH	NaOAc	4	99	98
6	PhC≡CH	NaOAc	3	100	100
7 ^f	PhC≡CH	NaOAc	3	78	73
8 ^g	PhC≡CH	NaOAc	3	98	96
9	C ₅ H ₁₁ C≡CH	NaOAc	4	100	95
10	C ₆ H ₁₃ C≡CH	NaOAc	5	100	92
11	HC≡CCH ₂ OH	NaOAc	4	100	71
12	HC≡CCH ₂ OAc	NaOAc	4	100	93

^a Alkyne (1 mmol), CuCl₂ (2 mmol), base (2 mmol), MeOH (1 ml), P_{CO₂} = 14 MPa, 40 °C. ^b Determined by GC analysis. ^c Did not add MeOH. ^d Only used MeOH (10 ml) as solvent. ^e P_{CO₂} = 7.5 MPa. ^f Added 1 mmol of CuCl₂. ^g Added 3 ml of MeOH.

in scCO₂ consisted of CuCl₂ (2 mmol), NaOAc (2 mmol), MeOH (1 ml) and CO₂ (14 MPa) at 40 °C.† Other terminal acetylenes besides phenylacetylene were employed successfully using the optimized conditions (entries 9–12, Table 1).

The coupling reaction gave low conversion and yield in pure scCO₂ (entry 1, Table 1), in which CuCl₂ and NaOAc cannot dissolve (entries 1, 4 and 7, Table 2). It has been reported that some organic or inorganic compounds, so-called ‘modifiers’, can be added to the supercritical fluids to increase its solvent power.¹¹ Our results indeed show that the presence of MeOH remarkably enhanced the rate of the reaction (entries 1 and 6, Table 1). We further examined the solubility of different reagents in different solvents in scCO₂ and the results were summarized in Table 2. MeOH, as modifier or co-solvent, increased the solubility of CuCl₂ and NaOAc in scCO₂ (entries 3, 6 and 8, Table 2).^{2,3,11,12} Increasing the amount of MeOH to 3 ml in the reaction, decreased the rate and the yield to a small extent. It is of interest to note that if only MeOH was used as solvent, both the rate and the yield decreased and the reaction was not clean (entry 2, Table 1). These results imply that scCO₂ and MeOH are of the same importance to the reaction. The low viscosity of scCO₂ allows the products (diacetylenes) to diffuse away from CuCl₂ and NaOAc, while the proper amounts of MeOH makes CuCl₂ and NaOAc partially dissolve in scCO₂, although excess MeOH may affect the diffusion of the products.

The pressure of CO₂ also affected the reaction rate to some extent. Our results indicate that a higher CO₂ pressure is preferable (entries 5 and 6, Table 1).

In earlier studies, when cupric chloride or cupric acetate was added as a promoter, an organic base (pyridine) was usually added to retain CuCl₂ or Cu(OAc)₂ in solution as complexes or solvates and to catch the acid liberated during the coupling reaction. In scCO₂, to our surprise, the coupling took place without base with higher conversion and yield than those in the presence of pyridine (entries 3 and 4, Table 1). When NaOAc

Table 2 Solubility of related reagents in different solvents^a

Entry	Reagents ^b	Solvent	Solubility
1	CuCl ₂	scCO ₂	insoluble
2	CuCl ₂	MeOH	soluble
3	CuCl ₂	MeOH/scCO ₂	partial
4	NOAc	scCO ₂	insoluble
5	NOAc	MeOH	partial
6	NOAc	MeOH/scCO ₂	partial
7	CuCl ₂ /NOAc	scCO ₂	insoluble
8	CuCl ₂ /NOAc	MeOH/scCO ₂	partial
9	CuCl ₂ /NOAc	MeOH ^c	soluble
10	Pyridine	scCO ₂	soluble
11	CuCl ₂ /pyridine	MeOH	partial ^d

^a The procedure for determining solubility in scCO₂: The desired amount of the related reagents was placed in a 25 ml stainless steel cell. The cell was sealed and filled with liquid carbon dioxide (14 MPa). The cell was then heated to 40 °C for the desired time and the solubility of the related reagents was monitored by viewing through a sapphire observation window.

^b Amounts of reagents: CuCl₂ = 269 mg, NaOAc = 164 mg, pyridine = 158 mg. Amounts of solvent: scCO₂ = 14 MPa, MeOH = 1 ml. ^c 10 ml.

^d The solubility of solid in this experiment is more than that of entry 8.

was added, the reaction gave a satisfactory result (entry 6, Table 1). It is clear that NaOAc is superior to pyridine in scCO₂. The results in Table 1 also show that a sufficient amount of cupric chloride is necessary for the Glaser coupling (entries 6 and 7, Table 1).

At least two reaction pathways had been proposed in earlier reports.^{8a,d} One involves a radical mechanism and the other formation of a cupric complex. We used two radical traps (*N*-*tert*-butylbenzylideneamine *N*-oxide and 2-methyl-2-nitrosopropane) in the reaction, but we did not detect any radicals.

Base on the results shown in Tables 1 and 2, we could conclude several points. (i) In scCO₂, the presence of NaOAc plays an important role in enhancing the reaction rate. (ii) A sufficient amount of cupric chloride is necessary for the Glaser coupling. (iii) the low viscosity of scCO₂ favors the oxidation coupling reaction of terminal acetylenes. (iv) Addition of a correct amount of MeOH can increase the dissolution of CuCl₂, and enhance the rate of the reaction.

In summary, we have observed that Glaser coupling reactions can proceed smoothly in scCO₂ in good yields. Of particular note is the fact that this new Glaser coupling reaction is more environmentally friendly than the traditional reaction and shows potential utility in industry. The mechanism and applications of the reaction are currently under investigation in our laboratory.

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Notes and references

† *Typical procedure*: To a mixture of CuCl₂ (2 mmol) and NaOAc (2 mmol) in an HF-25 autoclave, MeOH (1 ml) and alkyne (1 mmol) were added.

Liquid CO₂ was then transferred into the autoclave to the desired pressure. The reaction mixture was stirred at 40 °C for 3–5 h. After the reaction, the CO₂ was vented and the surplus was extracted with Et₂O. The conversion was determined by GC using an internal standard. The product was then purified by preparative TLC on silica gel using light petroleum–EtOAc (10:1) as eluent.

- 1 P. G. Jessop, T. Ikariya and R. Noyori, *Chem. Rev.*, 1999, **99**, 475.
- 2 L. Jia, H. Jian and J. Li, *Green Chem.*, 1999, 91.
- 3 L. Jia, H. Jiang and J. Li, *Chem. Commun.*, 1999, 985.
- 4 F. Bohlmann, F. T. Burkhardt and C. Zero, *Naturally Occurring Acetylenes*, Academic Press, London and New York, 1973.
- 5 L. Hansen and P. M. Boll, *Phytochemistry*, 1986, **25**, 285.
- 6 Y. S. Kim, S. H. Jin, S. L. Kim and D. R. Hahn, *Arch. Pharm. Res.*, 1989, **12**, 207.
- 7 H. Matsunaga, M. Katano, H. Yamamoto, H. Fujito, M. Mori and K. Tukata, *Chem. Pharm. Bull.*, 1990, **38**, 3480.
- 8 Review: (a) R. A. Raphael, E. C. Taylor and H. Wynberg, *Advances in Organic Chemistry*, Mack Printing CO, Easton, PA, New York, 1963, vol. 4, pp. 225–328; (b) W. S. Trahanovsky, *Oxidation in Organic Chemistry*, Academic Press, New York and London, 1973, vol. 5-B, p. 1; (c) M. Hudlicky, *Oxidation in Organic Chemistry*, ACS Monograph 186, Washington DC, 1990, p. 58; (d) H. G. Viehe, *Chemistry of Acetylenes*, Marcel Dekker, New York, 1969, p. 597; (e) K. Sonogashira, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 3, p. 551.
- 9 R. Rossi, A. Carpita and C. Bigelli, *Tetrahedron Lett.*, 1985, **26**, 523.
- 10 S. Kenkichi, T. Yasuo and H. Nobue, *Tetrahedron Lett.*, 1985, **26**, 523.
- 11 J. A. Darr and M. Poliakoff, *Chem. Rev.*, 1999, **99**, 495.
- 12 A. Francis, *J. Phys. Chem.*, 1954, **58**, 1099; J. B. Ellington, K. M. Park and J. F. Brennecke, *Ind. Eng. Chem. Res.*, 1994, **33**, 965.

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