Microwave Enhanced Glaser Coupling Under Solvent Free Conditions

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Received 26 October 2000

Abstract: A microwave enhanced, solvent free, Glaser coupling reaction has been developed. Self coupling of terminal alkynes on potassium fluoride-alumina in the presence of cupric chloride affords good yields of the corresponding diacetylenes.

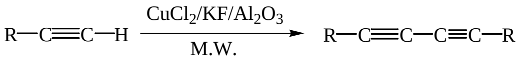
Key words: Glaser coupling, microwave irradiation, terminal alkynes, potassium fluoride on alumina, cupric chloride

Diacetylenes are very important in biological, polymer and material science.[1-3] A useful method for preparing diacetylenes involves a cupric salt promoted self-coupling reaction of terminal alkynes. In 1869, Glaser[4] first observed that terminal alkynes undergo oxidative coupling to form diacetylenes in the presence of Cu_2Cl_2,O_2, and NH_4Cl. Subsequent studies indicated that a variety of copper salts are effective mediators for the coupling reaction which is generally carried out in organic solvents such as methanol, acetone, pyridine, methyl cellosolve and toluene. These solvents often pose waste handling problems and the amines required in most Glaser reactions add to the environmental burden.

We have found alumina to be a particularly useful reagent in an organic synthesis because it can be modified in a variety of ways which enhance its reactivity.[5] Furthermore, alumina can be utilized to solve environmental problems associated with organic solvents. For example, using a commercially available alumina potassium fluoride mixture, to which we added palladium powder, we were able to carry out Suzuki and Sonogashira coupling reactions on a wide variety of aromatic moieties without the use of solvent.[6-8]

Microwave irradiation of organic reactions has also gained in popularity in recent years since microwaves were found to accelerate a wide variety of transformations.[9,10] Early experiments utilized solvents with high dielectric constants which permitted rapid heating of reaction solutions. In recent years, a number of reports have appeared in which the organic reagents are coated onto surfaces which themselves absorb little or no microwave energy; in these instances, the reaction species absorb the microwave energy but the bulk temperature of the reaction mixture tends to rise only modestly. This results in a relatively large energy savings as well as making it possible to carry out reactions in relative simple glassware such as open beakers and flasks.

We now wish to report a microwave enhanced, energy efficient modification of a solid-state Glaser reaction which enhances the reaction's eco-friendly attributes. The new methodology couples microwave irradiation with a solid-state, solvent free approach which leads to enhanced yields of the desired diacetylenes (Scheme 1).



$$R{-}C{\equiv}C{-}H \xrightarrow[\text{M.W.}]{CuCl_2/KF/Al_2O_3} R{-}C{\equiv}C{-}C{\equiv}C{-}R$$

Scheme 1

In our initial studies, we attempted to optimize the reaction conditions for the oxidative coupling of terminal alkynes. The results are summarized in Table 1. Phenylacetylene was chosen as the model compound for the optimization process.

Table 1 The effect of copper slats on the Glaser coupling of phenylacetylene[a]

Entry	Cu Salts	Base/Al_2O_3	Yields (%)[b]
1	—	KF/Al_2O_3	0
2	$CuCl_2$	KF/Al_2O_3	75
3	$CuCl_2$	K_2CO_3/Al_2O_3	74
4	$CuCl_2$	KOH/Al_2O_3	66
5	$CuCl_2$	Al_2O_3	52
6	$Cu(Ac)_2$	KF/Al_2O_3	22
7	$CuCO_3$•$Cu(OH)_2$	KF/Al_2O_3	41
8	Cu_2Cl_2	KF/Al_2O_3	42
9	CuI	KF/Al_2O_3	17
10	Cu_2Cl_2-$CuCl_2$ (1:2)	KF/Al_2O_3	70
11	CuI-$CuCl_2$ (1:2)	KF/Al_2O_3	74
12	CuI-Na_2BO_4 (1:2)	KF/Al_2O_3	9

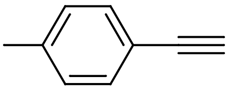
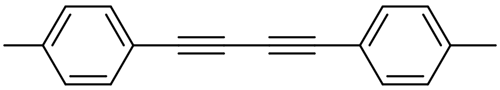
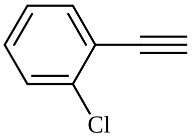
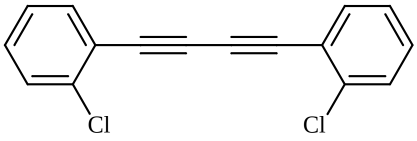
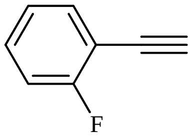
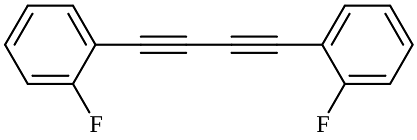
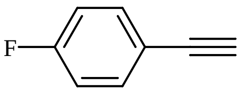
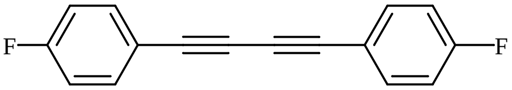
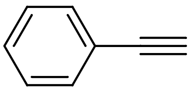
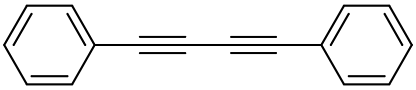
[a] Phenylacetylene (1 mmole), Cu salt (3.7 mmole), base (40% by weight)/Al_2O_3 (4 mmole); a 1000 watt microwave oven (Sharp Model R-4A38) was used at 30% power for 8 minutes.

[b] Isolated yield.

From Table 1, it is evident that the yield of the coupling reaction requires a copper salt. The efficiency of the Cu salt decreases in the order: $CuCl_2$>CuI-$CuCl_2$>CuCl-$CuCl_2$>Cu_2Cl_2> $CuCO_3$.$Cu(OH)_2$>$Cu(Ac)_2$>CuI. The use of Cu(I) in the presence of an oxidizing agent was not effective (Entry 12).

Synlett 2001, No. 1, 108–110 ISSN 0936-5214 © Thieme Stuttgart · New York

Table 2 Glaser Coupling Reaction of Terminal Alkynes[a]

Entry	Alkynes	Diacetylenes[b]	Yields (%)[c]
1	n-$C_8H_{17}C{\equiv}CH$	n-$C_8H_{17}C{\equiv}C{-}C{\equiv}CC_8H_{17}$-$n$	61
2	n-$C_6H_{13}C{\equiv}CH$	n-$C_6H_{13}C{\equiv}C{-}C{\equiv}CC_6H_{13}$-$n$	53
3			68
4			56
5			54[d]
6			63
7			75

[a] Reaction conditions: terminal alkyne (1 mmole), $CuCl_2$ (0.5 g, 3.7 mmole), KF/Al_2O_3 (40% by weight, 0.6 g), a 1000 watt microwave oven (Sharp Model R-4A38) was used at 30% power for 8 minutes for the reactions were halted after 2 minutes to allow the reaction to cool.

[b] All reaction products exhibit physical and spectral characteristics in accord with literature values.

[c] Isolated yield.

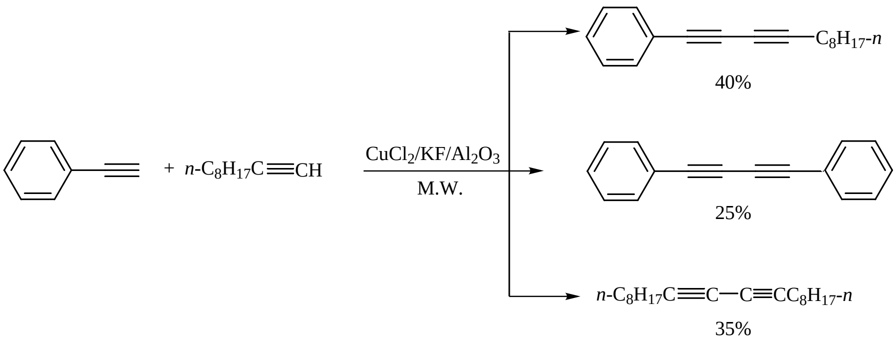
[d] Satisfactory elemental analysis was obtained.

The best reaction conditions for coupling were found to be $CuCl_2$ (3.7 mmole), KF/Al_2O_3 (40% by weight, 0.6 g), terminal alkyne (1 mmole) under microwave irradiation for 8 minutes. [Note: The reactions were stopped after two minutes to allow the mixture to cool and then were continued for six minutes.]

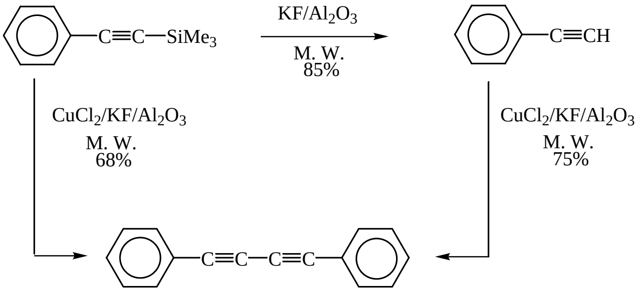
A variety of terminal alkynes were successfully coupled using the optimized reaction conditions.[11] The results are summarized in Table 2.

The date in Table 2 indicates that, under microwave irradiation and solvent free conditions, self-coupling of terminal alkynes, occurs smoothly to produce the desired diacetylenes in moderate to good yields. We also examined the cross-coupling reaction between two different terminal alkynes but a mixture of products was obtained (Scheme 2).

Since aryl alkynes are often generated from the corresponding trimethylsilyl reagents by bases such as potassium carbonate and potassium fluoride,[12] we examined the Glaser coupling of 1-phenyl-2-(trimethylsilyl)-acetylene on potassium fluoride-alumina in the presence of cupric chloride under microwave irradiation. The results shown that diphenylbutadiyne was formed in the one-pot reaction with moderate yield (68%), which was higher than that of a two step sequence (total 64%)(Scheme3).



Scheme 2



Scheme 3

In summary, we have demonstrated that Glaser coupling reactions proceed smoothly under solvent free conditions when aided by microwave irradiation. The advantages of this reaction are the mild, environmentally friendly reaction conditions, simple operation, and good yields.

Acknowledgement

We wish to thank the U. S. Department of Energy and the Robert H. Cole Foundation for support of this research.

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(11) The synthesis of diphenylbutadiyne is representative. Phenylacetylene (102 mg, 1.0 mmole) was added to a mixture of KF/Al_2O_3 (600 mg, 40% by weight) and cupric chloride (500 mg, 3.7 mmole) contained in a clean, dry 10 mL round-bottomed flask. The mixture was stirred at room temperature to ensure efficient mixting. The flask was then fitted with a septum (punctured by an 18 gauge needle), placed in the microwave and irradiated at 30% power for two minutes and then allowed to cool. The microwave irradiation was then continued for six minutes. After cooling, hexane (3 mL) was added and the slurry stirred at room temperature to ensure product removal from the surface. The mixture was filtered and the product was purified by flash chromatography to yield 76 mg of diphenylbutadiyne (75%).

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Article Identifier:
1437-2096,E;2001,0,01,0108,0110,ftx,en;S05800ST.pdf