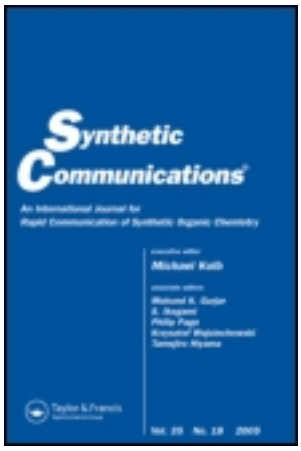

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Jin-Xian Wang [a], Zhanxiang Liu [a], Yulai Hu [a], Bangguo Wei [a] & Liqin Kang [a]

[a] Institute of Chemistry, Department of Chemistry, Northwest Normal University, 95 An Ning Road (E.), Lanzhou, 730070, China

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MICROWAVE-ASSISTED COPPER CATALYZED COUPLING REACTION OF ARYL HALIDES WITH TERMINAL ALKYNES

Jin-Xian Wang,* Zhanxiang Liu, Yulai Hu, Bangguo Wei, and Liqin Kang

Institute of Chemistry, Department of Chemistry, Northwest Normal University, 95 An Ning Road (E.), Lanzhou 730070, China

ABSTRACT

Coupling reaction of aryl halides with terminal alkynes using catalyst system of copper (I)-triphenylphosphine proceeds efficiently in the presence of potassium carbonate under microwave irradiation to give the corresponding unsymmetrical acetylenes in good yield.

INTRODUCTION

The palladium-catalyzed[1–4] coupling reaction of aryl halides with terminal alkynes is a useful tool for preparation of unsymmetrical acetylenes and now widely used for the synthesis of biologically active

*Corresponding author.

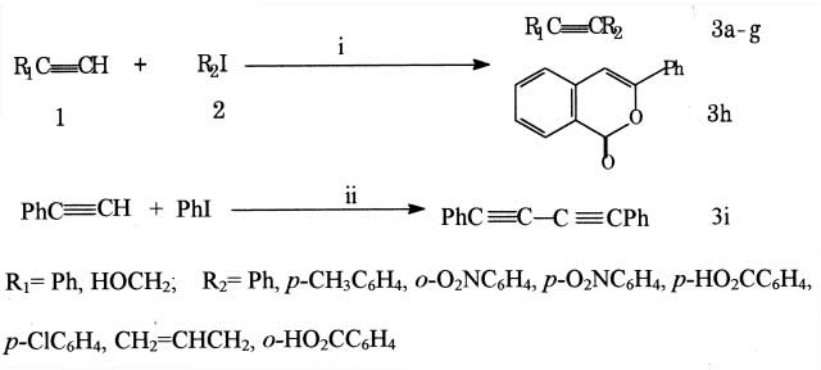
enyne-compounds.[5,6] Because of their importance, a number of methods have been developed for the synthesis of substituted acetylenes. The most effectively this reaction proceeds in the presence of catalytic amounts of palladium complex and cuprous iodide. For example: using $Pd(PPh_3)_2Cl_2$-CuI,[7–9] PdL_2Cl_2-CuI/sc CO_2,[10] $Pd(OAc)_2$-PPh_3,[1a] $Pd(PPh_3)_4$[11] as catalysts for the coupling reaction of aryl halides with terminal alkynes. A few examples of this reaction in aqueous medium have been reported.[8]

Generally the reaction proceeds under mild conditions in the presence of copper iodide, in anhydrous organic solvents involving the intermediate formation of a copper acetylide.[12–14] Most of these reactions involve stoichiometric amount of the copper catalyst.[15] Recently, Okuro et al.[16] have reported the reaction of aryl and vinyl halides with terminal alkynes proceeds efficiently in the presence of a catalytic amount of copper iodide using potassium carbonate as base to give the coupling products in good yield when an appropriate amount of triphenylphosphin or *n*-Bu_4NCl[3] are added. On the other hand, there have also been some reports on the allylation of terminal alkynes by copper(I) and phase transfer catalyzed.[17,18]

In recent years, microwave-induced rate acceleration technology is becoming a powerful tool in organic synthesis, because of milder reaction conditions, reduction of reaction time, enhanced selectivity and associated ease of manipulation. Some important reviews have been published.[19] Microwave irradiation has also been applied to several organic reactions. However, few practical applications have been devised for the coupling reaction in the presence of palladium.[20,21] There are no reports on the use CuI-PPh_3 as catalyst for the coupling reaction of aryl halides with terminal alkynes under microwave irradiation conditions.

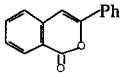
RESULTS AND DISCUSSION

We have now found that substituted acetylenes 3a–g can be obtained from aryl iodides 2 with terminal alkynes 1 using CuI-PPh_3 as catalyst under microwave irradiation conditions. This method is simple, rapid and affords good yield. The reactions are shown in Scheme 1 and results are summarized in Table 1. The results in Table 1 show that in the presence of CuI-PPh_3, a variety terminal alkynes have been converted to the corresponding unsymmetrical acetylenes in good yield under microwave irradiation conditions. Under these conditions, 2-iodobenzoic acid is converted exclusively



Scheme 1. Reagents and conditions: i, CuI-PPh_3, K_2CO_3, DMF, Ar, MWI, 375 W, 10 min; ii, CuI-PPh_3, K_2CO_3, DMF, MWI, 375 W, 10 min.

Table 1. Fast Copper-Catalyzed Coupling Reaction of Aryl Iodides with Terminal Alkynes Under Microwave Irradiation[a]

Entry	Product		Yield (%)[c]
1	PhC≡CPh	(3a)	91
2	*p*-$CH_3C_6H_4C$≡CPh	(3b)	84
3	*o*-$O_2NC_6H_4C$≡CPh	(3c)	83
4	*p*-$O_2NC_6H_4C$≡CPh	(3d)	90
5	*p*-$HO_2CC_6H_4C$≡CPh	(3e)	92
6	*p*-ClC_6H_4C≡CPh	(3f)	80
7	$HOCH_2C$≡CCH_2=$CHCH_2$	(3g)	80
8		(3h)	86
9	PhC≡C–C≡CPh	(3i)	65[b]

[a]The reactions were carried out in the presence of K_2CO_3 using CuI-PPh_3 as catalyst in DMF at 375 W for 10 min under argon. [b]Under the same conditions but without the Ar protection, the product is 3i. [c]Isolated yield.

to 3-phenylisocoumarin (3h). In the case of phenylacetylene with iodobenzene, However, under the some conditions but without the Ar protection, the product is 1,4-diphenyl-1,3-butadiyne 3i.

Using the synthesis of 3a as example, we have investigated the effect of different mole ratios on the reaction of phenylacetylene with iodoarenes

under microwave irradiation. The results showed that the best mole ratio is PhC=CH : PhI : CuI : PPh_3 : K_2CO_3 = 1.5 : 1.0 : 0.1 : 0.2 : 1.5. The yield of 3a is 91%. The efficiency of various solvents on the formation of 3a was studied using microwave irradiation. DMF was found to be an effective solvent for the reaction. The effect of various solvents in the synthesis of 3a is in the following order: DMF > DMSO > CH_3CN > EtOH > benzene. The results are summarized in Table 2. We have also investigated the effect of different catalysts on the reaction. It was found that the activities of the catalysts are

Table 2. Effect of Various Solvent on the Formation of (3a)[a,b,c]

Entry	Solvents	Dielectric Constant (ε)	Yield of (3a)[d] (%)
1	CH_3CN	37.5	82
2	DMF	36.5	91
3	DMSO	46.6	86
4	Benzene	2.3	10
5	EtOH	24.6	40

[a]The reaction was carried out in the presence of K_2CO_3 using CuI-PPh_3 as catalyst at a power level of 375 W for 10 min continuous irradiation under argon. [b]Unless indicated otherwise mol ratios PhC=CH : PhI : CuI : PPh_3 : K_2CO_3 = 1.5 : 1.0 : 0.1 : 0.2 : 1.5. [c]The reaction was monitored by TLC on silica gel. [d]Yield of isolated product.

Table 3. Effect of Catalyst (CuI-PPh_3) and Base on the Formation of (3a)[a]

Entry	Catalyst	Base	Yield of (3a)[b]
1	CuI-PPh_3	Na_2CO_3	90
2	CuI-PPh_3	NaOH	55
3	CuI-PPh_3	$NaHCO_3$	60
4	CuI-PPh_3	K_2CO_3	91
5	CuBr-PPh_3	K_2CO_3	82
6	CuCl-PPh_3	K_2CO_3	68
7	PPh_3	K_2CO_3	0

[a]The reaction was carried out in DNF at a power level of 375 W for 10 min under argon. [b]Isolated yield.

Table 4. The Effect of Microwave Irradiation Power[a]

Irradiation Power (W)	75	150	300	375	450	750
Yield (%)[b]	40	51	54	78	75	72

[a]The reaction was carried out in the presence of K_2CO_3 using CuI-PPh_3 as catalyst for 5 min continuous irradiation under argon. [b]Isolated yield.

Table 5. The Effect of Microwave Irradiation Time[a]

Irradiation Time (min)	2	5	10	15
Yield (%)[b]	22	78	90	90

[a]The reaction was carried out in the presence of K_2CO_3 using CuI-PPh_3 as catalyst at a power level of 375 W continuous irradiation under argon. [b]Isolated yield.

in the following sequence: CuI/PPh_3 > CuBr/PPh_3 > CuCl/PPh_3 > PPh_3. The results are summarized in Table 3.

We have also investigated the effects of irradiation power and time on the reaction. The results are summarized in Tables 4 and 5. It was found that the highest yield of compound 3a is obtained at a power level of 375 W for 10 min continuous irradiation.

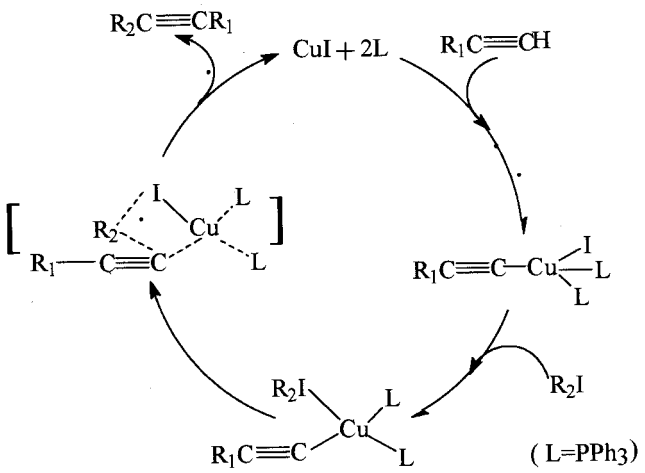
The impact of the microwave irradiation and conventional heating[3,9,14b,16] for the formation of compounds 3a–h has been compared and results are summarized in Table 6. The results showed that the synthesis of 3a–h under microwave irradiation were 48–144 times faster than under conventional reflux.

Mechanism

A possible mechanism[14b,18] for the coppe catalyzed coupling of terminal acetylenes with iodoarenes is described in Scheme 2. In the first step, the terminal acetylene reacts with CuI-PPh_3 in the presence of base to form the organometallic compound. Then high reactive organometallic compound enters reaction of cross-coupling with iodoarene to give aryl alkynyl derivative of Cu-PPh_3. This derivative is unstable and can easily regenerates the CuI and PPh_3 through the reductive elimination of substitution product. The CuI-PPh_3 is thus recycled in the reaction.

Table 6. Comparison of Time and Yields on the Formation of Compounds 3a–h Using Microwave and Conventional Heating

	Conventional Heating		Microwave Heating			
Product	t/min	Yield (%)	Power/W	t/min	Yield (%)	t_c/t_{mw}
3a	720	83	375	10	91	72
3b	1440	95	375	10	84	144
3c	600	84	375	10	83	60
3d	720	75	375	10	90	72
3e	600	85	375	10	92	60
3f	1440	92	375	10	80	144
3g	900	89	375	10	80	90
3h	480	91	375	10	86	48



Scheme 2.

EXPERIMENTAL

Microwave irradiation was carried out with a commercial microwave oven GlanzWp 750B at 2450 Hz. ^{1}H NMR spectra were recorded in $CDCl_3$ on a BRUKER PT 80A Spectrometer using tetramethylsilane as internal standard. Chemical shifts were reported as δ in ppm. IR spectra were measured with an Alpha centauri FI-IR spectrometer as KBr discs or film.

Mass spectra were recorded on a QP-1000A GC-MS using the electron impact mode (70 ev). Melting points were determined with an Electrothermal micromelting point apparatus and were uncorrected. All solvents were used without further purification. The remaining chemicals were obtained from commercial sources. All reactions were conducted under an argon atmosphere.

General Procedure

In the reaction flask were mixed iodobenene (1.02 g, 5 mmol), alkynes (7.5 mmol), CuI (0.09 g, 0.5 mmol), PPh_3 (0.262 g, 1 mmol) and K_2CO_3 (1.04 g, 7.5 mmol) in DMF (10 mL), then irradiated at 375 W for 10 min. After cooling, the product mixture was poured into 30 mL diethyl ether, then filtered the residue was washed with ether. The combine ether was washed with the saturated brine (3×10 mL) and dried over magnesium sulfate. The dried ethereal solution was concentrated. The crude product was purified by column chromatography on silica gel using petroleum/ethyl acetate (v/v 1 : 1) as the eluent.

Diphenylacetylene 3a: M.p. 61–62°C (lit.[22] 62.5°C); MS (*m*/*e*, %): 178 (M^+, 96%), 177 (100); IR ν (KBr): 3018, 1598, 1532, 1492, 984, 756, 688; ^{1}H-NMR ($CDCl_3$): 6.98–7.50 (m, 10H, ArH).

4-Methyldiphenylacetylene 3b: M.p. 71–72°C (lit.[23] 70.9–71.8°C); MS (*m*/*e*, %): 192 (M^+, 89), 191 (100), 177 (21); IR ν (KBr): 2857, 2160, 1593, 1509, 1483, 754, 689; ^{1}H-NMR ($CDCl_3$): 7.10–7.60 (m, 9H, ArH), 2.34–2.37 (s, 3H, CH_3).

2-Nitrodiphenylacetylene 3c: M.p. 43–44°C (lit.[14b] 43–44°C); MS (*m*/*e*, %): 223 (M^+, 100), 177 (25); IR ν (KBr): 2188, 1578, 1482, 1523, 1344, 947, 759, 687; ^{1}H-NMR ($CDCl_3$): 7.25–7.66 (m, 8H, ArH), 8.61–8.65 (m, 1H, ArH).

4-Nitrodiphenylacetylene 3d: M.p. 119–120°C (lit.[14b] 119–120°C); MS (*m*/*e*, %): 223 (M^+, 100), 177 (92); IR ν (KBr): 2170, 1592, 1511, 1347, 997, 764, 688; ^{1}H-NMR ($CDCl_3$): 7.17–7.82 (m, 7H, ArH), 8.07–8.18 (m, 2H, ArH).

4-Carboxyldiphenylacetylene 3e: M.p. 221–222°C (lit.[14b] 221–222°C); MS (*m*/*e*, %): 222 (M^+, 100), 205 (40), 177 (20); IR ν (KBr): 3075, 2600, 2197, 1604, 1484, 918, 952, 753, 690; ^{1}H-NMR ($CDCl_3$): 7.03–7.66 (m, 7H, ArH), 8.0–8.15 (m, 2H, ArH).

4-Chloridiphenylacetylene 3f: M.p. 82–83°C (lit.[24] 81.5–82); MS (*m*/*e*, %): 214 ($M^+ + 2$, 33), 212 (M^+, 100), 177 (40), 102 (33); IR ν (KBr): 2158, 1602, 1484, 1074, 958, 760, 693, 742; ^{1}H-NMR ($CDCl_3$): 7.91–7.82 (m, 2H, ArH), 7.17–7.80 (m, 9H, ArH).

5-Hexene-2-yn-ol 3g: Oil, b.p. 70–72°C/2.7 KPa (lit.[3] 70–72/2.7 KPa); MS (*m*/*e*, %): 96 (M^+, 17), 95 (15), 82 (13), 65 (100); IR ν (KBr): 3300, 2928, 2854, 2220, 1645, 990, 915; ^{1}H-NMR ($CDCl_3$): 1.6 (s, 1H, OH), 3.2 (d, 2H, $=CH_2$), 3.40 (t, 2H, $CCH_2=$), 4.03 (s, 2H, OCH_2), 5.90 (m, 1H, CH=).

3-Phenylisocoumarin 3h: M.p. 88–89°C (lit.[25] 89–91°C); MS (*m*/*e*, %): 222 (M^+, 100), 194 (50), 165 (36), 105 (28); IR ν (KBr): 1750, 1669, 1591, 1508, 964, 755, 685; ^{1}H-NMR ($CDCl_3$): 7.05 (s, 1H, HC=C), 7.16–7.51 (m, 8H, ArH), 8.20 (d, 1H, ArH).

1,4-Diphenyl-1,3-butadiyne 3i: M.p. 87–88°C (lit.[26] 88°C); MS (*m*/*e*, %): 214 (M^+).

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